

Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists as of March 31, 2020

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Introduction The first outbreak of the disease currently known as coronavirus disease 2019 (COVID-19) was recorded in December 2019 in Wuhan, China. A new *Betacoronavirus*, currently known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), turned out to be its etiological factor. Following the spread of the epidemic to all continents, the World Health Organization announced the COVID-19 pandemic on 11 March, 2020. Coronaviruses are a group of enveloped viruses containing single-stranded RNA with positive polarity. So far, 6 species of human pathogenic coronaviruses have been found to cause airway infections. Two of them, SARS-CoV and MERS-CoV, have been the cause of worldwide or local outbreaks in the last 20 years, which have been limited by sanitary and epidemiological control methods. SARS-CoV-2 spreads through droplet transmission as well as contaminated objects and surfaces. The virus is present in various body fluids (nose and throat secretion, sputum, stool, tears, blood). The average incubation period for COVID-19 is 5 days, but it can last up to 14 days. Its manifestations are often asymptomatic and mild with fever, coughing and dyspnea. In more advanced forms, it leads to interstitial inflammatory lesions in the lungs. In severe clinical cases, at the end of the first week from the initial

symptoms, the signs of acute respiratory failure develop, which leads to multiorgan failure and death of the patient. Mortality rates ranging from 0% to 8% vary from country to country and depend on the quality of health care, in particular the equipment and the availability of intensive care units, but perhaps also on many unknown human genetic factors and/or virus genetic mutability. Etiotropic treatment confirmed in clinical trials is not available. There are attempts to use drugs registered so far for other indications, but their effectiveness has not been confirmed either. Work on developing vaccines has begun, and it can bring results no earlier than in 2021.

Minimum requirements for units hospitalizing patients with SARS-CoV-2 infection

- The admission office should be closed to other patients and dedicated exclusively to patients referred with suspected SARS-CoV-2 infection.
- A distance of at least 2 meters between patients should be ensured in the waiting room of the admission office. In case of difficulties with arrangement of such rooms, it is advisable to prepare heated tents in front of the entrance to the building.
- Personal protective equipment (PPE) should include: overalls or long-sleeved waterproof

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Received: March 30, 2020.

Revision accepted: March 31, 2020.

Published online: March 31, 2020.

Pol Arch Intern Med. 2020;

130 (4): 352-357

doi:10.20452/pamw.15270

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aprons; safety goggles or visors; FFP2 or FFP3 respirator masks; gloves (optimally nitrile); caps and protective footwear if waterproof aprons are also used.

- The intensive care unit within the structures of the hospital or intensive care sites within the structures of the department of infectious diseases or temporarily adapted infectious diseases rooms should have respirators and extracorporeal membrane oxygenation secured with anesthesia personnel available.
- Computed tomography, or lung X-ray, or lung ultrasound should be available 24 hours, 7 days a week.
- Ensure access to the molecular diagnostics laboratory that allows to obtain results within a maximum of 24 hours from the sample collection, ideally up to 8 hours (in order to exclude infection in the setting of the admission office).
- There should be clear signs marking the access to the admission office limiting the possible contact of those with and without infection.

Diagnostic workup Molecular diagnostic workup

The diagnosis of active SARS-CoV-2 infection is based on real-time reverse transcriptase–polymerase chain reaction (RT-PCR). Persons who meet the criteria of the COVID-19 suspected case (see the Suspected case section) should be tested to detect genetic material of the virus.

Serological methods In the course of an epidemic, mass serological testing with rapid tests on request, especially for detecting IgM class antibodies, can be used to identify asymptomatic infections once other means of reducing the epidemic have been exhausted. Tests detecting IgG or IgM/IgG antibodies can be useful in epidemiological studies, for example, to estimate the number of people who have been in contact with the virus as well as for population studies. However, to definitively rule out or confirm SARS-CoV-2 infection, the RT-PCR test is required.

Rapid molecular testing A rapid molecular test for SARS-CoV-2 diagnostic workup recently registered by the Food and Drug Administration of the United States requires a diagnostic system that has been successful in recent years in the diagnosis of many infections (including hepatitis C virus and influenza). The performance of rapid molecular tests can be particularly useful in admission offices of infectious diseases departments and emergency rooms.

Criteria for diagnosing coronavirus disease 2019

Suspected case In order to perform tests to detect the genetic material of SARS-CoV-2, the following conditions for the COVID-19 suspicion need to be fulfilled:

- Acute respiratory infection with a sudden onset and at least 1 of the following symptoms: fever, coughing, dyspnea, or serological testing positive for antibodies.

- One or combination of the following:
 - Travel or residence in the last 14 days following the onset of the disease to the country or region where a local transmission of SARS-CoV-2 infection was recordedor
 - Close contact with a confirmed or probable COVID-19 case in the last 14 days
- or

- Severe illness requiring hospitalization in the absence of any other etiology that may explain the clinical image.

However, if a local transmission in a given area is documented, it is only required to fulfil the first condition. This means that all patients with symptoms of acute respiratory infection at the first contact with healthcare (primary care facility or hospital of any profile) should be treated as suspected and therefore should be tested to confirm the infection.

Probable case A diagnosis of COVID-19 is likely when an individual with symptoms of acute respiratory infection has a doubtful or ambiguous result of RT-PCR for SARS-CoV-2 or when the result of a pan-coronavirus test is positive.

Confirmed case Any person with SARS-CoV-2 infection confirmed by RT-PCR, regardless of the presence of clinical symptoms, is considered a confirmed case.

Clinical image Asymptomatic or mild type

- Absence of symptoms or mild upper respiratory tract complaints (fever, coughing, or shortness of breath), which may sometimes be accompanied by headaches, muscle pains, nausea, vomiting, diarrhea.
- Stable clinical image.

Diagnostic workup

- Diagnostic workup consist of testing for influenza and / or other pathogens responsible for upper respiratory tract infections.

Clinical monitoring in the hospital

- Clinical evaluation by physician and assessment of vital parameters (temperature, blood pressure, heart rate, respiratory count, Glasgow scale) 2 to 3 times a day.
- Pulse oximetry 2 to 3 times a day; the objective is to maintain oxygen saturation as measured by pulse oximetry (SpO₂) above 94%.

Clinical monitoring in the place of isolation

- Physician consultation should take place at least once a day (can be by phone).
- A nurse should evaluate the patient's general clinical condition and measure the temperature at least twice a day.

Virological monitoring

- Nose and throat swab RT-PCR testing for SARS-CoV-2 at least 14 days from the onset of

TABLE 1 Modified Early Warning Score (MEWS)

Score	3	2	1	0	1	2	3
Respiratory rate, breaths/min		≤8		9–14	15–20	21–29	>29
Heart rate, bpm		≤40	41–50	51–100	101–110	111–129	>129
Systolic blood pressure, mm Hg	≤70	71–80	81–100	101–199		≥200	
Hourly urine, ml/kg of body weight/h	Nil	<0.5					
Body temperature, °C		≤35	35.1–36	36.1–38	38.1–38.5	≥38.6	
Neurological symptoms				Alert	Responsive to voice	Responsive to pain	Unresponsive

symptoms, and in asymptomatic patients, at least 14 days from the swab signaling initial infection.

- If the first control test is negative, a second control test should be carried out after at least 24 hours.
- After a double negative result, the patient can be released from isolation or hospitalization if the clinical condition permits.
- If any of the 2 control results is positive, the test should be repeated at 7-day intervals until negative.

Imaging

- In general, imaging is not necessary.
- In case of persistent coughing and/or symptoms indicating lung involvement, a routine lung X-ray or lung computed tomography scan is advised.

Treatment

- Treatment should be solely symptomatic.

Stable patients with respiratory and/or systemic symptoms

- Modified Early Warning Score (MEWS) of less than 3 (TABLE 1)
- Patients with typical COVID-19 symptoms, due to the risk of clinical deterioration, require monitoring and action to accelerate the elimination of SARS-CoV-2 infection.
 - Exhaustion, asthenia, fever higher than 38 °C and coughing.
 - Clinical and radiological lung occupation.
 - Absence of clinical or laboratory respiratory failure.
 - These patients require hospitalization due to the risk of disease progression.

Diagnostic workup

- Examination for influenza and/or other pathogens responsible for upper respiratory tract infections.
 - Swabs for bacterial infections in the upper respiratory tract (avoid aerosol-generating procedures, which are risky for the personnel).
 - In case of persistent fever higher than 38 °C, perform blood cultures.

Clinical monitoring

- Clinical evaluation and assessment of vital signs (temperature, blood pressure, heart rate,

respiratory count, Glasgow scale) 2 to 3 times a day.

- Pulse oximetry 2 to 3 times a day; the objective is to maintain SpO₂ above 94%.
- Evaluation of the acid-base balance, especially on days 5 to 7 from the initial symptoms or in case of a sudden deterioration of the clinical condition.

Virological monitoring

- Perform virological monitoring as per asymptomatic and mild types described above.

Imaging

- Lung X-ray is the basis for the identification of lung lesions and can be performed with portable devices.
 - Computed tomography (without contrast) has a high sensitivity for detecting interstitial lesions, valuable together with the assessment of the acid-base balance in predicting deterioration.
 - Pulmonary ultrasound can be an easy method for early detection of pneumonia directly at the admission office.

Primary treatment Due to insufficient data resulting from lack of complete clinical trials usually required to register a drug for use for a particular indication, decisions on primary treatment should be made individually by the treating physician. Based on limited knowledge and availability of drugs in the therapy, the following may be considered:

- **Lopinavir / ritonavir** administered orally in a dose of 400/100 mg every 12 hours for 14 days **plus**
- **Chloroquine** administered orally usually in a dose of 250 mg (in justified cases, 500 mg) every 12 hours for 7 to 10 days (no longer than 10 days) or **hydroxychloroquine** administered orally with a loading dose of 400 mg every 12 hours and maintenance dose of 200 mg every 12 hours for 10 days.
 - Other drugs with a potential antiviral effect and a proven safety profile may be used (at least a phase 2 clinical trial or a medical experiment with a drug used for another indication).
 - It is not recommended to use drugs whose alleged efficacy has been verified in case studies or single reports not confirmed by other studies.

Supportive treatment

- Alternatively, antibiotic therapy based on an antibiogram or empirical broad-spectrum antibiotic therapy.
- Palliative treatment.
- Provide access to oxygen therapy, to be available in case of clinical deterioration.

Clinically unstable patients with respiratory failure

- MEWS of 3 to 4 ([TABLE 1](#))
- The patient demonstrates acute symptoms of respiratory tract involvement requiring close monitoring especially in days 5 to 7 from the initial symptoms in order to potentially provide intensive care.
- Clinical and/or laboratory signs of deterioration of respiratory and gas exchange capacity (respiratory disorders, high respiratory rate, dyspnea, low peripheral SpO₂ <90%)

Diagnostic workup

- Examination for influenza and/or other pathogens responsible for upper respiratory tract infections.
- Swabs for bacterial infections in the upper respiratory tract (avoid aerosol-generating procedures, which are risky for the personnel).
- In case of persistent fever higher than 38 °C, perform blood cultures.
- Extend the diagnostic workup depending on the clinical image (eg, for HIV).

Clinical and laboratory monitoring

- Closely monitor patient's clinical condition and evaluate vital signs (temperature, blood pressure, heart rate, respiratory count, Glasgow scale, SpO₂)
- Evaluate the acid-base balance, especially on days 5 to 7 from the initial symptoms or in case of a sudden deterioration of the clinical condition.
- Monitor D-dimers, ferritin, fibrinogen, C-reactive protein, triglyceride, lactate dehydrogenase, interleukin 6 (IL-6).
- Consult an intensive care specialist.

Virological monitoring

- Perform virological monitoring as per asymptomatic and mild types described above.

Imaging

- Lung X-ray is the basis for identification of lung lesions and can be performed with portable devices.
- Computed tomography (without contrast) has a high sensitivity for detecting interstitial lesions and evaluating their dynamics. It should be performed in every patient at this stage of the disease. Contrast radiology should only be performed to differentiate (eg, with pulmonary embolism).
- Pulmonary ultrasound can be an easy method for early detection of pneumonia directly at the admission office.
- Echocardiography is indicated in case of suspected acute heart failure due to respiratory failure.

Primary treatment Due to insufficient data resulting from lack of complete clinical trials usually required to register a drug for use for a particular indication, decisions on primary treatment should be made individually by the treating physician. Based on limited knowledge and availability of drugs in the therapy, the following may be considered:

- **Remdesivir** administered intravenously once a day with a loading dose of 200 mg and later maintenance dose of 100 mg for 10 days, or (if remdesivir is unavailable) lopinavir/ritonavir administered orally in a dose of 400/100 mg every 12 hours for 28 days

plus

- **Chloroquine** administered orally usually in a dose of 250 mg (in justified cases, 500 mg) every 12 hours for 7 to 10 days (not longer than 10 days), or hydroxychloroquine administered orally with a loading dose of 400 mg every 12 hours and maintenance dose of 200 mg every 12 hours for 10 days

plus

- **Tocilizumab** (in patients with elevated IL-6 concentration) administered intravenously in a dose of 8 mg/kg of body weight (maximally 800 mg) in a single dose (a 1-hour infusion). In the absence of improvement, the second dose may be repeated after 8 to 12 hours.

Alternative treatment

- Other drugs with a potential antiviral effect and a proven safety profile may be used (at least a phase 2 clinical trial or a medical experiment with a drug used for another indication).
- It is not recommended to use drugs whose alleged efficacy has been verified in case studies or single reports not confirmed by other studies.

Supportive treatment

- Alternatively, antibiotic therapy based on an antibiogram or empirical broad-spectrum antibiotic therapy.
- Symptomatic treatment.
- Oxygen therapy.
- Intravenous rehydration.
- Glucocorticoids in case of deterioration of respiratory function (necessary especially when tocilizumab is used):
 - **Methylprednisolone** administered intravenously in a dose of 1 mg/kg per day for 5 days, later 40 mg per day for 3 days, next 10 mg per day for 2 days,
 - or
 - **Dexamethasone** administered intravenously in a dose of 20 mg per day for 5 days, later 10 mg per day for 3 days, next 5 mg per day for 2 days.

Patient in critical condition (acute respiratory distress syndrome) Patient with MEWS of more than 4 ([TABLE 1](#)) in severe condition associated with deep respiratory failure and impairment of other vital functions:

- Acute respiratory distress syndrome (ARDS).
- Hypotension and shock.
- Multi-organ failure.
- Impaired consciousness.

Diagnostic workup

- Examination for influenza and/or other pathogens responsible for upper respiratory tract infections.
- Swabs for bacterial infections in upper respiratory tract (avoid aerosol-generating procedures which are risky for the personnel).
- In case of persistent fever higher than 38 °C, perform blood cultures.
- Extend the diagnostic workup depending on the clinical image (eg, for HIV).

Clinical and laboratory monitoring

- Close monitoring in the intensive care unit.
- Nose and throat swab RT-PCR testing for SARS-CoV-2 until negative.
- Evaluation of the acid-base balance, especially on days 5 to 7 after the first symptoms or in case of a sudden deterioration of the clinical condition.
- Monitoring of D-dimers, ferritin, fibrinogen, C-reactive protein, triglyceride, lactate dehydrogenase, IL-6.

Imaging

- Computed tomography (without contrast) has a high sensitivity for detecting interstitial lesions and evaluating their dynamics. It should be performed for every patient at this stage of the disease. Contrast radiology should only be performed in case of differentiation (eg, with pulmonary embolism).
- Echocardiography is indicated in suspected acute heart failure due to respiratory failure.

Primary treatment Due to insufficient data resulting from lack of complete clinical trials usually required to register a drug for a particular indication, decisions on primary treatment should be made individually by the treating physician. Based on limited knowledge and availability of drugs in the therapy, the following may be considered:

- **Remdesivir** administered intravenously once a day with a loading dose of 200 mg and later maintenance dose of 100 mg for 10 days, or (if remdesivir is unavailable) lopinavir/ritonavir administered orally in doses of 400/100 mg every 12 hours for 28 days,

plus

- **Chloroquine** administered orally in a dose of 500 mg every 12 hours for 7 to 10 days, or hydroxychloroquine administered orally with a loading dose of 400 mg every 12 hours and maintenance dose of 200 mg every 12 hours for 10 days,

plus

- **Tocilizumab** administered intravenously 8 mg/kg of body weight (maximally 800 mg) in a single dose (a 1-hour infusion). In the absence

of improvement, the second dose may be repeated after 8 to 12 hours.

Alternative treatment

- Other drugs with a potential antiviral effect and a proven safety profile may be used (at least a phase 2 clinical trial or a medical experiment with a drug used for another indication).
- It is not recommended to use drugs whose alleged efficacy was verified in case studies or single reports not confirmed by other studies.

Supportive treatment

- Early mechanical ventilation.
- Extracorporeal membrane oxygenation in the case of refractory hypoxemia, independently of invasive mechanical ventilation.
- Alternatively, antibiotic therapy based on an antibiogram or empirical broad-spectrum antibiotic therapy.
- Glucocorticoids (necessary especially when tocilizumab is used):
 - **Methylprednisolone** administered intravenously in a dose of 1 mg/kg of body weight per day for 5 days, later 40 mg per day for 3 days, next 10 mg per day for 2 days,
 - or
 - **Dexamethasone** administered intravenously in a dose of 20 mg per day for 5 days, later 10 mg per day for 3 days, next 5 mg per day for 2 days.

Drugs with potential antiviral or anti-inflammatory effects that may be considered

- **Favipiravir**: registered for influenza in Japan, no research for SARS-CoV-2.
- **Ruxolitinib**: the European Medicines Agency registered for marrow fibrosis and polycythemia vera; planned research for COVID-19.
- **Oseltamivir**: the European Medicines Agency registered for influenza, no conclusive research for SARS-CoV-2 infection; it cannot be ruled out that the improvement in clinical status was due to the elimination of the influenza virus in coinfection.
- **Opaganib**: preparations for phase 2 of the trial.
- **Verdinexor**: preparations for phase 2 of the trial.

For more information on drugs used in ongoing trials, see <https://www.cebm.net/oxford-covid-19/covid-19-registered-trials-and-analysis/>.

Medicines with insufficient repeatable efficacy results against SARS-CoV-2

- **Azithromycin**: available data indicate a possible weak nonspecific anti-inflammatory effect. There are currently no randomized clinical trials on azithromycin in COVID-19. Azithromycin may be considered in COVID-19 in situations justified by accompanying bacterial infections on principles concerning antibiotic therapy.

Need for approval of the Bioethics Committee

- Due to no indication for COVID-19 or SARS-CoV-2 infection in the summaries of product

characteristics, it is necessary to obtain the approval of a bioethical committee to use the following drugs in the setting of a medical experiment:

- Lopinavir / ritonavir
 - Hydroxychloroquine
 - Remdesivir
 - Tocilizumab
- The section entitled Medicines with potential antiviral or anti-inflammatory effects that may be considered includes a list of drugs that may be considered for use in clinical trials, early access, or compassionate use. In such cases, in addition to other administrative requirements, it is necessary to obtain the approval of a bioethical committee, which should be informed of the state of knowledge about the efficacy of the drug in COVID-19.

Drug interactions When combining therapeutic options, attention should be paid to potential drug interactions. Decisions can be made on the basis of the information at <http://www.covid19-druginteractions.org/>.

SUPPLEMENTARY MATERIAL

The Polish version of these recommendations is available as supplementary material at www.mp.pl/paim.

ARTICLE INFORMATION

NOTE A correction to the list of authors was made after approval for publication. Krzysztof Simon was added as the eighth author (April 10, 2020).

CONFLICT OF INTEREST None declared.

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HOW TO CITE Flisiak R, Horban A, Jaroszewicz J, et al. Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists as of March 31, 2020. *Pol Arch Intern Med*. 2020; 130: 352-357. doi:10.20452/pamw.15270

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