



Agency for Health Technology Assessment and Tariff System

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# COVID-19 recommendations

***Polish diagnostic, therapeutic and organisational  
recommendations for the care of individuals infected  
with SARS-CoV-2 or exposed to a SARS-CoV-2 infection***

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<sup>1</sup> Conflict of interest: The members of the expert panel were required to submit a declaration of conflict of interest in accordance with the ADAPTE toolkit (The ADAPTE Collaboration (2009). The ADAPTE Process: Resource Toolkit for Guideline Adaptation. Version 2.0. <http://www.g-i-n.net>).

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### ***List of abbreviations***

|                 |   |
|-----------------|---|
| <b>229E</b>     | Human coronavirus 229E                                    |
| <b>A&amp;E</b>  | Accident and Emergency Unit                               |
| <b>AICU</b>     | Anaesthesiology and Intensive Care Unit                   |
| <b>AGP</b>      | aerosol-generating procedures                             |
| <b>ALT</b>      | alanine transaminase                                      |
| <b>AMBU</b>     | self-inflating bag resuscitation                          |
| <b>AOTMiT</b>   | Agency for Health Technology Assessment and Tariff System |
| <b>APS</b>      | antiphospholipid syndrome                                 |
| <b>ARDS</b>     | acute respiratory distress syndrome                       |
| <b>AST</b>      | aspartate transaminase                                    |
| <b>BAL</b>      | bronchoalveolar lavage                                    |
| <b>BALF</b>     | bronchoalveolar lavage fluid                              |
| <b>BiPAP</b>    | biphasic positive airway pressure                         |
| <b>BNP</b>      | B-type natriuretic peptide                                |
| <b>CAPS</b>     | catastrophic antiphospholipid syndrome                    |
| <b>CDC</b>      | Centers for Disease Control and Prevention                |
| <b>CI</b>       | confidence interval                                       |
| <b>COP</b>      | cryptogenic organising pneumonia                          |
| <b>COVID-19</b> | Coronavirus Disease 2019                                  |
| <b>CPAP</b>     | continuous positive airway pressure                       |
| <b>CQ</b>       | chloroquine   |
| <b>CRP</b>      | C-reactive protein  |
| <b>CT</b>       | computed tomography                                       |
| <b>DOAC</b>     | direct oral anticoagulants                                |
| <b>DSES</b>     | District Sanitary-Epidemiological Station                 |
| <b>EBV</b>      | Epstein-Barr virus  |
| <b>ECDC</b>     | European Centre for Disease Prevention and Control        |
| <b>ECG</b>      | electrocardiography                                       |
| <b>ECMO</b>     | ExtraCorporeal Membrane Oxygenation                       |
| <b>ELISA</b>    | enzyme-linked immunosorbent assay                         |
| <b>EMA</b>      | European Medicines Agency                                 |
| <b>EMS</b>      | Emergency Medical Services                                |
| <b>EMSC</b>     | National Emergency Medical Services (EMS) Coordinator     |
| <b>ER</b>       | Emergency room  |

|             |  |
|-------------|--|
| <b>ERT</b>  | Emergency Response Team                              |
| <b>eWUŚ</b> | Electronic Verification of the Beneficiaries' Rights |
| <b>FDA</b>  | Food and Drug Administration                         |
| <b>FiO2</b> | fraction of inspired oxygen                          |
| <b>Hb</b>   | haemoglobin  |
| <b>HCQ</b>  | hydroxychloroquine                                   |
| <b>HFNC</b> | high-flow nasal cannula                              |
| <b>HFNO</b> | high-flow nasal oxygen                               |
| <b>HFOV</b> | high frequency oscillatory ventilation               |
| <b>HIV</b>  | human immunodeficiency virus                         |
| <b>HKU1</b> | Human coronavirus HKU1                               |
| <b>HR</b>   | hazard ratio   |
| <b>HRCT</b> | high-resolution computed tomography                  |
| <b>ICU</b>  | Intensive care unit                                  |
| <b>IgA</b>  | Immunoglobulin A                                     |
| <b>IgG</b>  | Immunoglobulin G                                     |
| <b>IgM</b>  | Immunoglobulin M                                     |
| <b>IH</b>   | Infectious Hospital                                  |
| <b>IL-6</b> | Interleukin 6  |
| <b>INR</b>  | international normalised ratio                       |
| <b>ITT</b>  | intention-to-treat                                   |
| <b>LDH</b>  | lactate dehydrogenase                                |
| <b>LFTs</b> | liver function tests                                 |
| <b>MD</b>   | mean difference                                      |
| <b>MEWS</b> | Modified Early Warning Score                         |
| <b>NAAT</b> | nucleic acid amplification testing                   |
| <b>NGAL</b> | neutrophil gelatinase-associated lipocalin           |
| <b>NGS</b>  | next generation sequencing                           |
| <b>NHS</b>  | National Health Service                              |
| <b>NIV</b>  | non-invasive ventilation                             |
| <b>NL63</b> | Human coronavirus NL63                               |

|  |  |
|--|--|
| <b>NMV</b>                             | non-invasive mechanical ventilation                        |
| <b>NNT</b>                             | number needed to treat                                     |
| <b>NT-proBNP</b>                       | N-terminal pro B-type natriuretic peptide                  |
| <b>OC43</b>                            | Human coronavirus OC43                                     |
| <b>OR</b>                              | odds ratio   |
| <b>PaO<sub>2</sub></b>                 | arterial blood oxygen partial pressure                     |
| <b>PaO<sub>2</sub>/FiO<sub>2</sub></b> | oxygenation index  |
| <b>PCR</b>                             | polymerase chain reaction                                  |
| <b>PEEP</b>                            | positive end-expiratory pressure                           |
| <b>PH</b>                              | Primary Healthcare   |
| <b>PPE</b>                             | personal protective equipment                              |
| <b>PVC</b>                             | polyvinyl chloride   |
| <b>RA</b>                              | rheumatoid arthritis                                       |
| <b>RCT</b>                             | randomised controlled trial                                |
| <b>RESM</b>                            | Regional Emergency Medical Services (EMS) Station          |
| <b>RNA</b>                             | ribonucleic acid   |
| <b>RR</b>                              | relative risk  |
| <b>rRT-PCR</b>                         | reverse- transcription real-time polymerase chain reaction |
| <b>RTG</b>                             | X-ray examination  |
| <b>RT-PCR</b>                          | reverse-transcription polymerase chain reaction            |
| <b>SA</b>                              | Swab ambulance   |
| <b>SARS-CoV-2</b>                      | severe acute respiratory syndrome coronavirus 2            |
| <b>SIH</b>                             | Specialist Infectious Hospital                             |
| <b>SPC</b>                             | Summary of Product Characteristics                         |
| <b>SpO<sub>2</sub></b>                 | oxygen saturation of haemoglobin                           |
| <b>SSC</b>                             | Surviving Sepsis Campaign                                  |
| <b>TV</b>                              | tidal volume   |
| <b>USG</b>                             | ultrasound   |
| <b>WHO</b>                             | World Health Organisation                                  |

*This document was commissioned by the Minister for Health based on a commission of 27 March 2020 concerning the development of a proposal for a comprehensive, multi-speciality set of key recommendations on the organisation and practice guidelines regarding diagnosis and treatment of medical care for patients suffering from a SARS-COV-19 virus infection, based on available scientific evidence.*

*To implement this project, the Agency appointed 7 Expert Panels, comprising of outstanding Polish specialists in the fields of anaesthesiology and intensive care, infectious diseases, laboratory diagnostics, epidemiology, microbiology, virology, pulmonology and radiology. The work of the Panels was coordinated by the Steering Committee, composed of the Presidium of the AOTMiT's Transparency Council, which was responsible for finalisation of the document. The recommendations were based on the few available original publications, an analysis of guidelines issued by international organisations and scientific societies as well as opinions of Polish experts.*

*The works were conducted with an active substantive participation of Maciej Miłkowski, Deputy Minister of Health and Grzegorz Juszczak, the Director of the National Institute of Public Health – National Institute of Hygiene. The Agency's analysts, who systematically reviewed the available publications in world literature, also contributed to the development of this paper.*

*I would like to thank all involved in the development of the recommendations for their extraordinary commitment despite the enormous amount of material to be covered and the fast pace of work necessitated by special circumstances.*

*Roman Topór-Mądry*

*PRESIDENT*

*of the Agency for Health Technology Assessment and Tariff System*

## INTRODUCTION

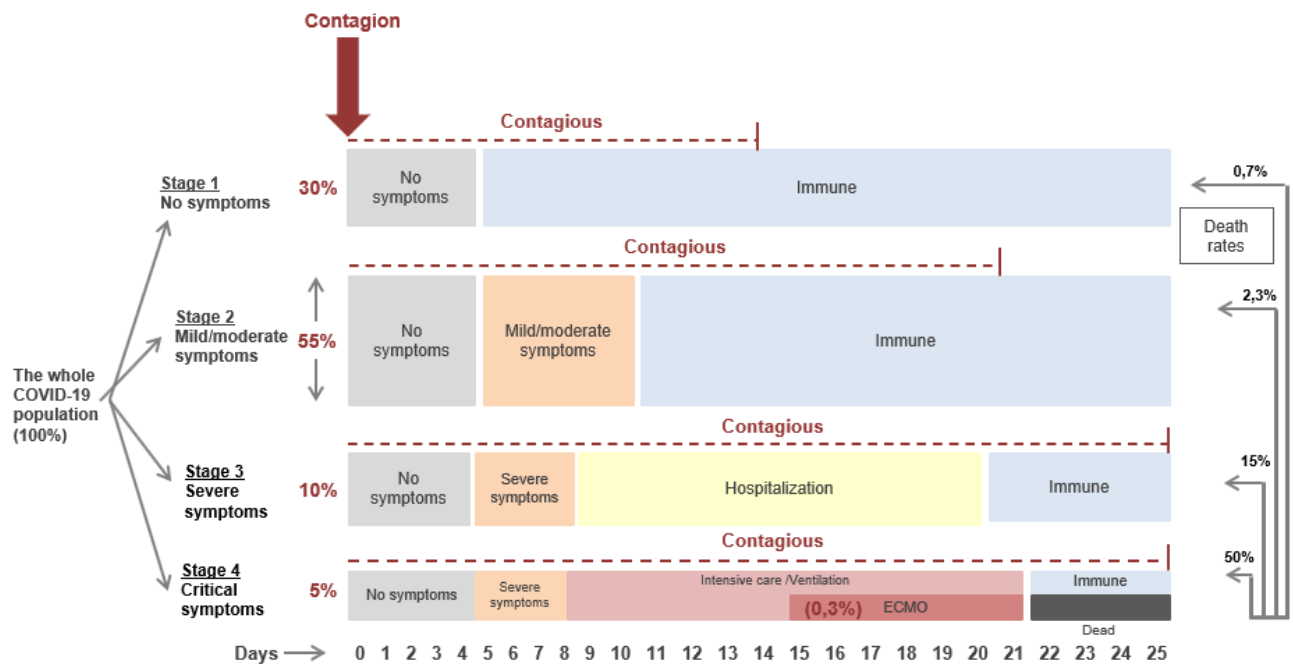
*These recommendations cover diagnosis and treatment, including controversial pharmacotherapy of coronavirus infection. The primary role in the treatment of COVID-19 is played by efficient oxygen therapy methods which have been discussed separately for infection, pulmonary and internal medicine wards. The recommendations for intensive care, where patients with the most severe condition are treated, are particularly important. Furthermore, recommendations concerning the protection of the medical personnel against virus infections are especially noteworthy. Each part consists of detailed recommendations and a justification or commentary, including a critical review of the data obtained from published works along with the source reference. To ensure transparency, descriptions of the scientific evidence are provided in the form of tables.*

*Unfortunately, so far there is no convincing scientific evidence confirming the efficacy of any drug in COVID-19 treatment with the exception of heparin which inhibits clotting. The recommendations indicate that possible treatment consists in the use of: convalescent serum, tocilizumab (which blocks the IL-6 receptor), remdesivir, lopinavir/ritonavir, favipiravir and chloroquine or hydroxychloroquine. Due to the lack of reliable confirmation of their greater effectiveness compared to no treatment and in view of the dangerous adverse effects, we believe that they can only be used in hospital settings, as part of clinical trials.*

*We are currently publishing the first version of the Recommendations. Considering the dynamically changing situation of the pandemic and the constant influx of new publications, the Recommendations will be supplemented, modified and adapted to the current organisational and medical needs in Poland. Any suggestions concerning what topics should be expanded or improved are welcome, as we will be publishing the next, second version in several days' time. We also encourage you to send links to recommendations with regard to the performed procedures and medical specialities. Do not hesitate to contact us with any comments or suggestions via e-mail at: [wytiecznecovid19@aotm.gov.pl](mailto:wytiecznecovid19@aotm.gov.pl).*

*The Steering Committee*

21 April 2020



**Figure 1.** Overview of the course of COVID-19 depending on the severity.

The graph available publicly in the Internet has been modified. Data based on the following sources:

1. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Lauer SA et al. Ann Intern Med. 2020 Mar 10;
2. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. Neil M Ferguson et al. Imperial College COVID-19 Response Team. 16 March 2020;
3. Viral dynamics in mild and severe cases of Covid-19. Yang Liu et al. The Lancet, March 19, 2020;
4. Verity R., Okell L.C., Dorigatti I. et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. The Lancet Infectious Diseases, March 30, 2020;
5. Oral information from University Hospital Regensburg in Germany (April 2020)

## **PART I**

# **DIAGNOSTIC AND THERAPEUTIC RECOMMENDATIONS**

# 1. DIAGNOSTICS

## 1.1. Clinical diagnostics

The adopted definition of a COVID-19 case is that defined by the World Health Organisation (WHO), which was also adapted by the European Centre for Disease Prevention and Control (ECDC)<sup>1,2</sup>.

### Identification criteria of COVID-19 – definitions

|                       | <b>Definition</b>   |
|-----------------------|---|
| <b>Suspected case</b> | <p>Meeting the following joint conditions set out in points A and B constitutes the basis for a suspected COVID-19 infection and warrants the testing for detection of SARS-CoV-2 genetic material:</p> <p><b>A.</b></p> <p>Sudden-onset acute respiratory infection and at least one of the following symptoms: fever, coughing, dyspnoea.</p> <p><b>B.</b></p> <ul style="list-style-type: none"><li>a) history of travel or residence to the region where local transmission of SARS-CoV-2 infection was recorded in the last 14 days prior to the disease onset, or</li><li>b) close contact with a confirmed or probable COVID-19 case in the last 14 days or</li><li>c) severe condition requiring hospitalisation, in the absence of any other aetiology that could explain the observed clinical presentation.</li></ul> <p><i>If a local transmission in the given area is recorded, only conditions in point A need to be met. Consequently, patients with symptoms of an acute respiratory infection, diagnosed at first contact with healthcare services (in a primary healthcare facility or in any type of hospital), should be treated as a suspected case and thus be subjected to a COVID-19 test to determine whether the patient is indeed infected.</i></p> |
| <b>Probable case</b>  | <p>A COVID-19 diagnosis is likely when a person with symptoms of acute respiratory infection has a doubtful or ambiguous result of an rRT-PCR (reverse-transcription real-time PCR) test of SARS-CoV-2 genetic material or when the rRT-PCR result of a pan-coronavirus test is positive OR when an epidemiological history, imaging results, and clinical signs are typical of COVID-19 in the absence of laboratory confirmation by rRT-PCR.</p>  |
| <b>Confirmed case</b> | <p>Any person with laboratory, rRT-PCR confirmation of a SARS-CoV-2 infection, regardless of clinical symptoms.</p>   |

### Most common clinical symptoms of a SARS-Cov-2 infection

Although the symptoms of COVID-19 vary, the most common ones observed in SARS-COV-2 patients include:

- fever (83–99%),
- cough (59–82%),
- fatigue (44–70%).

The less common symptoms are:

- dyspnoea (31–40%),
- expectoration of sputum (28–33%),
- myalgia and arthralgia (11–35%),
- headaches (10–15%),
- rhinitis and sore throat (14–15%),
- haemoptysis (<10%),
- nausea, vomiting (5.8%),
- diarrhoea (3.8–4.2%).<sup>3,4,5,6,7</sup>

In the elderly and people with concurrent diseases, the onset of fever and respiratory symptoms may be delayed compared to other patients<sup>8,9</sup>. In a Chinese study involving 1,099 hospitalised patients, fever was observed in only 44% of patients upon admission to hospital and in 89% of patients during hospitalisation. In some COVID-19 patients, gastrointestinal symptoms such as diarrhoea and nausea were observed before the onset of fever and lower respiratory tract symptoms<sup>10</sup>. Moreover, loss of the sense of smell and taste has been reported, even before the occurrence of respiratory symptoms<sup>11</sup>. In severe cases of COVID-19, the following organs can also be damaged: liver, intestines, kidneys, cardiovascular system and brain. Vascular endothelium damage can lead to thrombosis.<sup>12</sup> 20% of Italian COVID-19 patients had skin rashes: urticaria, morbilliform, vesiculobullous, varicella-like, minor skin petechiae and acral ischaemia.<sup>13,14</sup>

Several studies have found that the symptoms of COVID-19 in children are similar to those observed in adults, but are usually milder and occur in a lower percentage of patients.<sup>15</sup>

### Degree of severity of disease

The Modified Early Warning Score (MEWS) was among the scales used to assess the severity of COVID-19.

**Table 1. Modified Early Warning Score (MEWS)**

| Points                                | 3        | 2     | 1       | 0         | 1                 | 2                | 3           |
|---------------------------------------|----------|-------|---------|-----------|-------------------|------------------|-------------|
| respiration rate (min <sup>-1</sup> ) |          | ≤ 8   |         | 9–14      | 15–20             | 21–29            | > 29        |
| heart rate (min <sup>-1</sup> )       |          | ≤ 40  | 41–50   | 51–100    | 101–110           | 111–129          | > 129       |
| systolic blood pressure (mmHg)        | ≤ 70     | 71–80 | 81–100  | 101–199   |                   | ≥ 200            |             |
| urinary output (mL/kg/h)              | < 10mL/h | < 0.5 |         | > 0.5     |                   |                  |             |
| body temperature (°C)                 |          | ≤ 35  | 35.1–36 | 36.1–38   | 38.1–38.5         | ≥ 38.6           |             |
| neurological symptoms                 |          |       |         | Conscious | Reacting to voice | Reacting to pain | No reaction |

### Level 1 – asymptomatic or oligosymptomatic

**Symptoms:** No symptoms or mild upper respiratory tract symptoms (fever, coughing without dyspnoea) that may sometimes be accompanied by headaches, myalgia, nausea, vomiting, diarrhoea. Hb saturation in percutaneous measurement (SpO<sub>2</sub>) >94%; stable clinical condition.

| <b>Recommendations</b>   |
|--|
| 1.1.1. <b>Diagnostics:</b> Testing for influenza is recommended. Imaging or biochemical tests are not required. In case of persistent cough and/or symptoms suggestive of lung involvement, a chest X-ray or CT scan is recommended. [expert consensus]  |
| 1.1.2. <b>Clinical monitoring:</b> <b>While a patient in this condition</b> requires isolated treatment, hospitalisation is not needed. The following steps should be taken in isolation: The general condition of the patient should be assessed and his/her temperature, pulse and blood pressure should be measured twice a day. [expert consensus] |

### Level 2 – symptomatic without signs of respiratory failure (Modified Early Warning Score (MEWS) <3 points)

**Symptoms:** Fatigue, asthenia, fever >38°C, coughing and dyspnoea. Clinical and radiological features of lung involvement. Due to the risk of clinical deterioration, the patient requires monitoring and measures to accelerate the elimination of a SARS-CoV-2 infection. No clinical or laboratory features of respiratory failure (SpO<sub>2</sub> >90-92%).

| <b>Recommendations</b>  |
|---|
| 1.1.3. <b>Diagnostics:</b> Testing for influenza and/or other pathogens responsible for respiratory tract infections (aerosol-generating procedures should be avoided, as they put the healthcare personnel at risk). In case of persistent fever exceeding 38°C,– blood cultures need to be performed. Laboratory tests: complete blood count with leukocyte differential count and platelet count, CRP, procalcitonin, glucose, creatinine, ALT, bilirubin, LDH, INR, D-dimer, cardiac troponin; determination of IL-6 level should also be considered. Imaging tests: chest X-ray, CT, ultrasound scan (for detailed recommendations, see below). [expert consensus] |
| 1.1.4. <b>Clinical monitoring:</b> Requires hospitalisation due to the risk of disease progression. Monitoring in hospital settings: temperature, blood pressure, heart rate, number of breaths, pulse oximetry – 2-3 times a day. Assessment of arterial blood gas and acid-base balance, in particular within 5-7 days following the onset of symptoms or in the event of a sudden clinical deterioration. [expert consensus]   |

### Level 3 – severe pneumonia with respiratory failure / pre-ARDS (MEWS score: 3-4 points)

**Symptoms:** Clinical and laboratory symptoms of respiratory failure and gas exchange deterioration (dyspnoea, increased respiratory rate, decreased SpO<sub>2</sub> < 90-92%). The patient demonstrates acute symptoms of respiratory system involvement requiring close monitoring, particularly between day 5 and 7 after the first symptoms occur in order to possibly provide intensive care. No ARDS symptoms, septic shock, multi-organ failure or consciousness disorders are observed.

### Recommendations

**1.1.5.Diagnostics:** Testing for influenza and other pathogens responsible for respiratory tract infections (aerosol-generating procedures should be avoided, as they put the healthcare personnel at risk). In the case of persistent fever exceeding 38°C, blood cultures need to be performed. Whether in-depth diagnostics should be performed depends on the clinical presentation (e.g. for HIV). Laboratory tests: complete blood count with leukocyte differential count and platelet count, CRP, procalcitonin, assessment of arterial blood gas and acid-base balance, glucose, ferritin, IL-6 level, creatinine, ALT, AST, amylase, albumin, bilirubin, creatinine, LDH, lactates, INR, D-dimer, cardiac troponin, BNP, NT-proBNP. Imaging tests: chest X-ray, CT, ultrasound scan (for detailed recommendations, see below). [expert consensus]

**1.1.6.Clinical monitoring:** Close clinical monitoring and assessment of vital signs (temperature, blood pressure, heart rate, number of breaths, Glasgow scale, SpO<sub>2</sub>). Assessment of arterial blood gas and acid-base balance. Echocardiography is indicated if acute heart failure is suspected. An intensivist should be consulted. [expert consensus]

## Level 4 – ARDS / multi-organ failure (MEWS >4 points)

**Symptoms:** Patient in a severe condition, with respiratory failure and impairment of other vital functions: acute respiratory distress syndrome (ARDS), sepsis and septic shock, multi-organ failure. The Berlin definition specifies three degrees of ARDS severity: mild: 200 mmHg < PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH<sub>2</sub>O, or in non-ventilated patients; moderate 100 mmHg < PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 200 mmHg (with PEEP ≥ 5 cmH<sub>2</sub>O in non-ventilated patients); severe: PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 100 mm Hg (with PEEP ≥ 5 cmH<sub>2</sub>O)<sup>16</sup>.

### Recommendations

**1.1.7.Diagnostics:** Testing for influenza and other pathogens responsible for respiratory tract infections (aerosol-generating procedures should be avoided, as they put the healthcare personnel at risk). In the case of persistent fever exceeding 38°C, blood cultures need to be taken. Whether in-depth diagnostics should be performed depends on the clinical presentation (e.g. for HIV). Laboratory tests: complete blood count with leukocyte differential count and platelet count, CRP, IL-6 level, procalcitonin, assessment of arterial blood gas and acid-base balance, glucose, ferritin, creatinine, ALT, AST, amylase, albumin, bilirubin, creatinine, LDH, lactates, INR, D-dimer, APTT, cardiac troponin, BNP, NT-proBNP. Imaging tests: chest X-ray, ultrasound scan, and in justified cases chest CT scan (for detailed recommendations, see below). [expert consensus]

**1.1.8.Clinical monitoring:** Close clinical monitoring and assessment of vital signs in ICU conditions. Assessment of arterial blood gas and acid-base balance. If acute heart failure is suspected, echocardiography is indicated. [expert consensus]

### Justification:

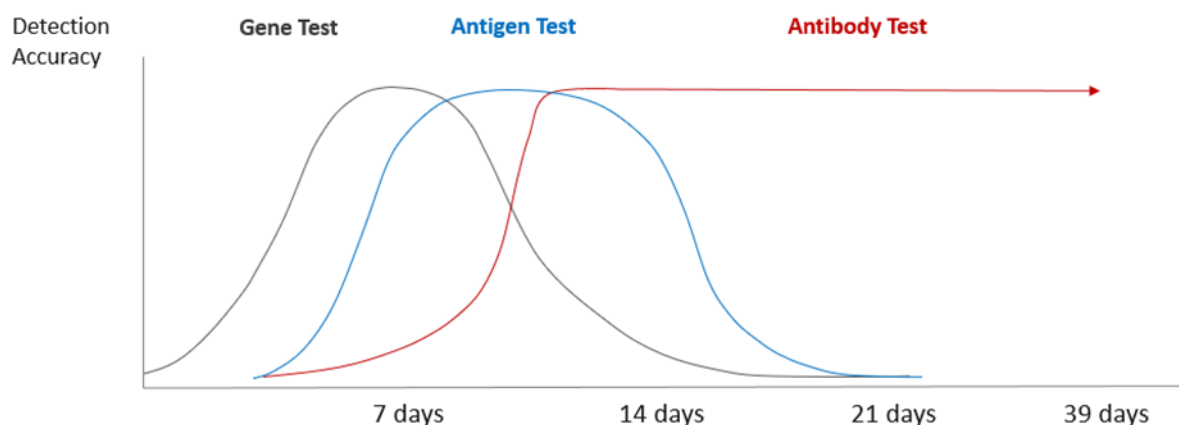
Studies have demonstrated that 83% of patients hospitalised for COVID-19 had lymphopaenia. In addition, lymphopaenia, neutrophilia, increased ALT, AST and LDH activity, high CRP and ferritin concentrations may be associated with greater severity of the disease. Upon admission to the hospital,

procalcitonin concentration may be normal; however, it usually increases in patients who are eligible for admission to the ICU<sup>17,18,19,20</sup>. Increased concentrations of D-dimer, IL-6 and lymphopaenia upon hospital admission may be associated with a higher risk of death<sup>21</sup>.

The recommendations are based on a critical assessment of scarce scientific evidence, mainly from China, combined with the consensus of a multidisciplinary Expert Panel.

## 1.2. Laboratory diagnostics

Below we present a diagram showing the ideas of the three types of tests discussed in the chapter below. The main test used to detect infections is a genetic test to determine the presence of viral genetic material in a nasopharyngeal swab. An antigen test detects virus protein if there is enough virus protein in the collected material. It may be faster and cheaper than the genetic test, but there is a controversy over its usefulness and its parameters must be checked before it being used more commonly. The third curve illustrates tests used to detect the immunological reaction of an infected person producing antibodies against the virus.



**Figure 2. Schematic illustration of the sequence of occurrence of the three test types discussed in the text. Accuracy of diagnostic tests in different disease stages. [based on materials provided by the antigen test manufacturer – PCL Antigen Detection Kit, South Korea] The chart also illustrates the reason for using different tests in different stages of COVID-19.**

### 1.2.1. Molecular testing of the viral genetic material

#### **Recommended rules for the collection and transport of molecular test material**

The recommended rules for the collection and transport of molecular test material are specified in the “Principles for the collection and transport of rRT-PCR test material for SARS-CoV-2” guidelines developed by the National consultant for medical microbiology – Katarzyna Dzierżanowska-Fangrat – and Regional Consultants for medical microbiology; they constitute an Annex<sup>22</sup> hereto.

## Molecular diagnostics (detection of viral genetic material)

| <b>Recommendations</b>  |
|---|
| 1.2.1.1. Safety rules for working with biological material must be strictly observed in laboratories working with infectious COVID-19 samples. As a minimum, BSL2 conditions, BSC2 chambers and personal protective equipment with FFP2 masks must be provided. To reduce the risk of infecting the staff, efforts should be made to implement automated nucleic acid isolation. [expert consensus] |
| 1.2.1.2. Molecular methods which detect the genetic material of the virus (NAAT-nucleic acid amplification testing) are the basis for diagnosing SARS-CoV-2 infections. The method of choice is rRT-PCR. [moderate strength of recommendation]  |
| 1.2.1.3. RRT-PCR tests should be performed in laboratories included on the Ministry of Health's list of COVID-19 laboratories. [expert consensus]   |

### **Justification:**

According to the identified scientific evidence, the basic technique for diagnosing SARS-CoV-2 infections is rRT-PCR (reverse-transcription real-time PCR)<sup>23</sup>. Isothermal amplification methods can constitute an attractive alternative. The detection of the presence of viral genetic material is possible only in the active phase of the disease when replication occurs in the tissues from which the material was taken. One advantage of molecular tests is the possibility of confirming the infection at an early phase when the antibody production has not yet taken place and to exclude active replication after the disease<sup>24</sup>.

Limitations of molecular techniques in the diagnosis of SARS-CoV-2 infections include the fact that it is a time-consuming and complicated method<sup>25</sup>. Rapid molecular tests are usually based on cassette technologies using rRT-PCR and isothermal technology and can be used at the patient's bedside.

| <b>Recommendations</b>   |
|--|
| 1.2.1.4. In urgent cases, rapid molecular tests for viral RNA can be performed. [expert consensus]   |
| 1.2.1.5. Although sequencing technologies, including next generation sequencing (NGS), can be useful in scientific research, as time-consuming and costly techniques they do not constitute the basis for diagnosing COVID-19. [expert consensus]                                      |
| 1.2.1.6. If the availability of molecular tests is limited, priority should be given to samples taken from patients with respiratory failure or dynamic clinical deterioration, as well as in emergency situations, regardless of whether associated with COVID-19. [expert consensus] |
| 1.2.1.7. Priority should also be given to diagnostics of the broadly understood medical personnel working with COVID-19 patients and patients who may be carriers of the virus and who manifest symptoms typical of COVID-19. [expert consensus + position of the Steering Committee]  |

**Justification:**

Given the time-consuming and complex procedure of existing rRT-PCR tests, rapid molecular tests (a result available in 15-45 minutes) can become an important diagnostic tool, especially in emergency cases<sup>26,27</sup>.

The sensitivity of molecular testing depends on the infection phase (the highest respiratory tract viral load is observed 4-10 days from symptom onset), the type of material collected and the manner in which the material is collected and transported (the recommended collection and transport methods constitutes a separate annex)<sup>28</sup>. Limitations of using rapid molecular tests (point-of-care tests) concern mainly the capacity and specificity of the method.

| <b>Recommendations</b>  |
|---|
| 1.2.1.8. The recommended diagnostic materials are nasopharyngeal swabs, swabs collected simultaneously from the throat and nasal mucosa, as well as from the lower respiratory tract – sputum (only if the patient coughs in a non-induced manner), tracheal aspirates or BAL. [expert consensus] |

**Table 2. The percentage of positive results reported in studies identified in the course of a systematic search of medical information databases (PubMed via Medline, last updated 4 May 2020) in which the diagnostic value of the RT-PCR method was assessed depending on the biological material tested**

| <b>Tested material</b>                                      | <b>Percentage of positive results<sup>29</sup></b>              |
|---|---|
| BAL   | 78.6% (11/14) <sup>30,31</sup> – 100% (12/12) <sup>32,33</sup>  |
| Sputum  | 48.68% (148/304) <sup>34</sup> – 100% (13/13) <sup>35,36</sup>  |
| Saliva  | 52.8% (38/72) <sup>37,38</sup> – 81.9% (59/72) <sup>39,40</sup> |
| Nasopharyngeal swab   | 19% (67/353) <sup>41</sup> – 68% (57/84) <sup>42</sup>          |
| Lingual swab  | 36.3% (33/91) <sup>43</sup>                                     |
| Oral swab   | 40% (4/10) <sup>44</sup>  |
| Oropharyngeal swab  | 7.6% (27/353) <sup>45</sup> – 44.2% (23/52) <sup>46</sup>       |
| Nasopharyngeal aspirate / nasopharyngeal swab / throat swab | 64.7% (22/34) <sup>47</sup> – 88.2% (30/34) <sup>48</sup>       |
| Nasal swab  | 16.4% (9/55) <sup>49</sup> – 76% (9/12) <sup>35,50</sup>        |
| Throat swab   | 11.1% (1/9) <sup>51,52</sup> – 61.3% (12/12) <sup>53,54</sup>   |
| Fibrobronchoscope brush biopsy                              | 46% (6/13) <sup>55</sup>  |
| Faeces  | 9.83% (24/244) <sup>56</sup> – 58% (46/79) <sup>57</sup>        |
| Rectal swab   | 10% (12/120) <sup>58</sup>                                      |
| Blood   | 1% (3/307) <sup>59</sup> – 3.03% (4/132) <sup>60</sup>          |
| Urine   | 0% <sup>61</sup>  |
| Plasma/blood  | (0/13) <sup>62</sup> – 11.5% (10/87) <sup>63</sup>              |

**Justification:**

The sensitivity of molecular tests in particular types of material is shown in the table below:

**Table 3. Sensitivity of molecular tests depending on the type of biological material collected<sup>64</sup>; in view of the uncertainty regarding the reliability of the report, the data should be considered as preliminary and require verification**

| Type of material               | Percentage of positive results |
|--------------------------------|--------------------------------|
| BAL                            | 93% (14/15);                   |
| <b>Sputum</b>                  | <b>72% (72/104);</b>           |
| <b>Nasal swabs</b>             | <b>63% (5/8);</b>              |
| Fibrobronchoscope brush biopsy | 46% (6/13);                    |
| Pharyngeal swabs               | 32% (126/389);                 |
| Faeces                         | 29% (44/153);                  |
| Blood                          | 1% (3/307);                    |
| Urine                          | 0% (0/72);                     |

#### Diagnostic materials collected from the lower airways

| <b>Recommendation</b>   |
|---|
| 1.2.1.9. Sputum may be used as a diagnostic material only in patients with cough and spontaneous expectoration. Inducing sputum for diagnostic purposes is not recommended due to the high risk of transmission of an infected aerosol. [high strength of recommendation] |

**Justification:**

Procedures associated with sputum induction for diagnostic purposes are recognised as aerosol-generating and associated with an increased risk of coronavirus transmission<sup>65</sup>.

#### Interpretation of molecular test results

Molecular methods allow for the detection of a number of SARS-CoV-2 genes, including N, E, S, RdRP and ORF1ab<sup>66</sup>.

| <b>Recommendations</b>  |
|---|
| 1.2.1.10. According to the WHO <sup>2</sup> , detection of genetic material, allowing for discrimination of a single gene, is deemed sufficient to confirm an infection in areas where COVID-19 community transmission occurs. [expert consensus, WHO recommendations]. In Poland, detecting at least 2 virus genes remains a condition for confirming a SARS-CoV-2 infection. Detection of a single gene confirms only a probable case and requires a laboratory verification. The |

<sup>2</sup> [https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-\(2019-ncov\)](https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov))

|   |
|---|
| criteria required for a laboratory confirmation of a COVID-19 case in Poland have been specified by the Chief Sanitary Inspector <sup>3</sup> .   |
| 1.2.1.11. Molecular diagnostic procedures require appropriate laboratory validation, and the result should be interpreted in line with the test manufacturer's instructions. [expert consensus]   |
| 1.2.1.12. A positive result is indicative of a SARS-CoV-2 infection; an inconclusive result does not exclude or confirm an infection. In such a case, another sample collected from the patient after 24-48 hours should be examined. [expert consensus]  |
| 1.2.1.13. A single negative result does not exclude the infection and should not be considered the only diagnostic criterion, especially in cases where the clinical presentation is indicative of a COVID-19 infection or where the patient has had close unprotected contact with a person with confirmed COVID-19, regardless of the type and intensity of the presented clinical symptoms. [expert consensus]   |
| 1.2.1.14. In the case of hospitalised patients with a negative result in the first-time molecular test, the test should be repeated in the following situations: <ul style="list-style-type: none"> <li>a) in the event of a high probability of an infection, determined on the basis of the collected epidemiological history, clinical presentation and the result of the chest imaging – another examination should be ordered within 24-48 hours after collecting the first sample.</li> <li>b) if the respiratory symptoms exacerbate – another examination should be ordered within 24-48 hours after collecting the first sample</li> <li>c) if the patient requires intubation and collecting material from the lower respiratory tract is possible. [expert consensus]</li> </ul> |
| 1.2.1.15. Whenever performed incorrectly, the test should always be repeated (e.g. due to improper collection or storage of the material) – another test should be ordered immediately. [expert consensus]  |

**Justification:**

The content of the recommendations is based on expert consensus and literature<sup>67,68,69</sup>.

**Virological monitoring in persons with confirmed infection**

| <b>Recommendations</b>   |
|--|
| 1.2.1.16. The follow-up should be performed after at least 14 days from obtaining the first positive result. If the result is negative, the test should be repeated after $\geq 24$ hours. Two subsequent negative results indicate a high probability that the virus has been eliminated from the respiratory tract. If either result is positive, the tests should be repeated at 7-day intervals until two consecutive negative results at 24-hour intervals have been obtained. [expert consensus] |

**Justification:**

According to CDC's analyses, a single negative SARS CoV-2 test result (especially if obtained from an upper respiratory tract sample) does not exclude a SARS-CoV-2 infection<sup>70</sup>.

<sup>3</sup> (<https://gis.gov.pl/aktualnosci/definicja-przypadku-na-potrzeby-nadzoru-nad-zakazeniami-ludzi-nowym-koronawirusem-sars-cov-2/>)

## **Virus monitoring in the health care personnel after an unsafe contact with a person infected with SARS-CoV-2**

| <b>Recommendations</b>   |
|--|
| 1.2.1.17. High-risk exposure means direct contact with an infected person during which the healthcare professional was not equipped with appropriate personal protective equipment. [expert consensus]   |
| 1.2.1.18. A healthcare professional with no clinical symptoms may undergo a molecular test after at least 7 days following the aforementioned exposure, and if the result is negative, authorising return to work may be considered. Further clinical observation and body temperature measurements should be continued despite obtaining a negative result. [expert consensus]. |

### **Justification:**

A recommendation based on an expert consensus, resulting from the current epidemiological situation.

### **1.2.2. Antigenic tests to detect viral proteins**

Tests used to detect SARS-CoV-2 protein antigens are usually immunochromatographic or based on the ELISA technology. Their advantages are low costs and short time required to perform the test, while their disadvantages include the possibility of cross-reaction with other common coronaviruses, low diagnostic sensitivity and lack of clinical validation. Comparative studies with molecular tests must be conducted to assess clinical utility of antigenic tests.<sup>71</sup>

| <b>Recommendations</b>   |
|--|
| 1.2.2.1. Until clinical validation is performed, using qualitative immunochromatographic tests detecting anti-SARS-CoV-2 antibodies is not recommended. [expert consensus] |
| Remark of the Steering Committee: the diagnostic reliability of one of the antigen tests is currently being assessed in Poland.  |

### **Justification:**

This recommendation was based on an expert consensus, resulting from the available data on antigen tests.

### 1.2.3. Serology tests used to determine the virus antibody concentration/titre

| <b>Recommendations</b>  |
|---|
| 1.2.3.1. The material for serological tests, collected in accordance with the applicable recommendations, is blood serum or plasma. <sup>72</sup> The type of anticoagulant used for plasma is determined depending on the recommendations of the specific reagent kit manufacturer used to determine the concentration / titre of anti-SARS-CoV-2 antibodies. <ul style="list-style-type: none"><li>• The recommended storage temperature of the material for serological tests is 2-8°C (≤5 days) or –70°C (&gt;5 days). [expert consensus]</li></ul> |
| 1.2.3.2. The primary indications for serological tests include: conducting epidemiological investigations and retrospective diagnostics of SARS-CoV-2- infections, estimating the number/percentage of individuals exposed to the virus, as well as population studies. [expert consensus]  |
| 1.2.3.3. While a positive serological test result may be indicative of contact with the coronavirus, it should be interpreted with caution.   |
| 1.2.3.4. Positive serological results should not be used as the basis for diagnoses or for infection phase reports. A SARS-CoV-2 infection can be confirmed only by molecular testing. [expert consensus]   |
| 1.2.3.5. Serological tests of the so-called twin sera may be used to identify asymptomatic individuals, monitor treatment of patients with COVID-19 symptoms (for detecting seroconversion) and to assess post-infection exposure. This procedure requires obtaining 2 serum samples tested at two-week (or longer) intervals. [expert consensus].  |

#### **Justification:**

The primary indication for the use of serological tests is conducting epidemiological investigations and retrospective diagnostics of SARS-CoV-2- infections, estimating the number/percentage of individuals exposed to the virus, as well as population studies<sup>73</sup>.

Serological diagnostics allows for detecting the presence of antibodies and may be particularly important in people with asymptomatic or mild symptoms<sup>74,75</sup>. The determination of the optimal time to carry out serological tests is related to the phenomenon of the so-called “serological window” (in the case of COVID-19, 7-14 days)<sup>76</sup>.

Serological tests should be considered as complementary to molecular methods<sup>77</sup> (they are used to assess the immune response of persons who have had contact with the virus).

Negative results of serological tests do not exclude a SARS-CoV-2 infection, as the delay time of antibody synthesis may be >7 days, and sensitivity for test groups within 10 days of the symptoms was only 50-66%<sup>78,79</sup>.

Positive serological results should not be used as the basis for diagnoses or for infection phase reports. Positive results may be related to past or ongoing infections with coronaviruses other than SARS-CoV-2, such as coronavirus HKU1, NL63, OC43 or 229E or other viruses including adenoviruses, EBV, CMV, or the presence of autoantibodies and rheumatoid factor and post-vaccination antibodies (influenza). A SARS-CoV-2 infection can be confirmed only by molecular testing<sup>80</sup>.

Serological tests of the so-called twin sera may be used to identify asymptomatic individuals, monitor people after exposure to SARS Cov-2 and to treat patients with COVID-19 symptoms (and detect seroconversion). For this purpose, serological tests are carried out on serum collected during the first

week after the disease onset (first serum sample) and after 2-4 weeks (second serum sample). A similar serological sampling scheme is recommended for people without COVID-19 symptoms, with documented or highly probable contact with an infected person (e.g. healthcare personnel) and to monitor the recovery process of people treated with COVID-19. In such a case, serological tests are carried out on serum collected as soon as possible (first serum sample) and after 2-4 weeks (second serum sample)<sup>81</sup>.

| <b>Recommendations</b> |  |
|------------------------|--|
| 1.2.3.6.               | There is no complete data assessing the clinical utility of immunochemical tests for anti-SARS-CoV-2 IgM and IgA antibodies (only manufacturer registration data is available) <sup>82</sup> . [expert consensus]  |
| 1.2.3.7.               | Until diagnostic reliability improves, using qualitative immunochromatographic tests detecting anti-SARS-CoV-2 antibodies is not recommended. [expert consensus]   |
| 1.2.3.8.               | Using properly validated immunochemical diagnostic tests characterised by high sensitivity and diagnostic specificity (the classic ELISA technique and its modifications, dedicated to automated analysers or chemiluminescence techniques, detecting specific anti-SARS-CoV-2 antibodies using an automatic detection system is recommended for determining the concentration/titre of anti-SARS-CoV-2 antibodies (since relying only on visual assessment is not objective). At least one antigen used in the test for detecting antibodies should originate from the S region of the Sars-CoV-2 virus. [expert consensus] |
| 1.2.3.9.               | The presence of IgG anti-SARS-CoV-2 antibodies, in combination with a negative molecular test result, may constitute grounds for certifying that the patient underwent an infection and is now cured. [expert consensus]   |

#### **Justification:**

The predictive value of currently available serological tests is mainly based on manufacturers' registration data, therefore no complete data evaluating the clinical utility of immunochemical tests for anti-SARS-CoV-2 IgM and IgA antibodies are available<sup>83</sup>. The results of available scientific studies indicate that the diagnostic value of these serological tests varies.

Similarly, rapid immunochromatographic tests (the so-called cluster tests) to detect the presence of antibodies have limited diagnostic value in the early phase of SARS-CoV-2 infections.

These tests, due to their low sensitivity and diagnostic specificity, also entail a high risk of obtaining false negatives and false positives, therefore the use of rapid qualitative immunochromatographic tests is not recommended.

The determination of the concentration/titre of anti-SARS-CoV-2 antibodies can be carried out using properly validated immunochemical diagnostic tests characterised by high sensitivity and diagnostic specificity (classical ELISA technique<sup>4</sup> and modifications, dedicated to automatic chemiluminescence analysers) that detect specific anti-SARS-CoV-2 antibodies using an automatic detection system (because visual assessment alone is not very objective). At least one antigen used in the test for detecting antibodies should originate from the S region of the Sars-CoV-2 virus <sup>84</sup>. The presence of IgG

<sup>4</sup> The sensitivity and specificity values for the tests to determine the concentration/titre of antibodies reported in the studies vary depending on the type of assessed antibodies. In Xiang 2020, sensitivity and specificity values of Elisa-based antibody detection tests in patients with a confirmed COVID-19 infection were 77.3% and 100%, respectively for IgM antibodies; 83.3% and 95.0% for IgG antibodies. In patients with a confirmed COVID-19 infection, the sensitivity and specificity values for IgM antibodies were 87.5% and 100%, respectively and for IgG antibodies – 70.8% and 96.6%. Xiang F, Wang X, et.al Antibody Detection and Dynamic Characteristics in Patients with COVID-19. Clin Infect Dis. 2020 Apr 19. pii: ciaa461. doi: 10.1093/cid/ciaa461.

anti-SARS-CoV-2 antibodies, in combination with a negative molecular test result, may constitute grounds for certifying that the patient underwent an infection and is now cured.

### Interleukin 6 (IL-6)

| <b>Recommendations</b>  |
|---|
| 1.2.3.10. Determining IL-6 levels should be considered in particular before tocilizumab administration, and then 8-12 hours after the first dose, to help decide on the next dose. [expert consensus] |
| 1.2.3.11. IL-6 and D-dimer concentration have prognostic significance and can, therefore, be determined at an earlier stage, i.e. in patients who scored 2 on the MEWS scale [expert consensus]       |

#### **Justification:**

The studies on the SARS-CoV-2 infection course suggest hyperactivation of cytotoxic T lymphocytes – humoral response – with interleukin 6 (IL-6) secretion as one of the inflammatory response mediators. Increased activity of IL-6 is a mediator of respiratory failure, shock and multi-organ failure; it indicates the occurrence of a “cytokine storm”.

Testing of the IL-6 level in serum is useful as a predictive test for the severe course of the infection.

The following results or events have predictive value on the patient's clinical deterioration:

1. IL-6 > 80 pg/mL AND/OR
2. rapid daily increases of IL-6 levels, i.e. multiple increases of IL-6 levels during the day,
3. an increase in d-dimer concentration,
4. decrease in haemoglobin oxygen saturation (SaO<sub>2</sub>).

For the dependence of IL-6 over time, see Zhou 2020<sup>85</sup> (n = 191, survivors vs. non-survivors, Figure 2) and Yuan 2020<sup>86</sup> (n = 94, patients discharged from hospital, mild vs. moderate vs. severe, antiviral treatment was applied, Figure 2). Diagnostic test regarding the patient's clinical deterioration based on IL-6 and/or d-dimer levels see Gao 2020<sup>87</sup> (n = 43, test sensitivity "IL-6 OR d-dimer" 93.3%, test specificity 5; Optimum cut-off level for IL-6 24.3 pg/mL, 3.3 *Analysis by ROC*).

## 1.3. Diagnostic imaging

Diagnostic imaging in COVID19 includes the following possible methods: chest X-ray, computed tomography (CT) of the chest, as well as chest and lung ultrasound.

### Chest X-ray

| <b>Recommendations</b>  |
|---|
| <b>Indications</b>  |
| 1.3.1. No imaging tests are necessary in asymptomatic cases or in the case of mild upper respiratory tract symptoms (fever, cough, mild dyspnoea). [expert consensus]                       |
| 1.3.2. If there are clinical indications for lung assessment (persistent cough and/or symptoms suggestive of lung involvement), a chest X-ray may be performed as a first-line examination. |

|  |
|--|
| Despite the non-specific X-ray image, this test, along with a comprehensive clinical evaluation,– may be helpful in diagnosing COVID-19. [expert consensus]  |
| 1.3.3. Control chest X-rays, both in clinically stable and unstable patients, should be kept to a minimum and performed only in cases requiring assessment of disease progression, where the result of the examination may affect the patient's treatment. [expert consensus]  |
| 1.3.4. Bedside X-ray is the recommended method to be used in severe patients with acute respiratory distress syndrome (ARDS) in whom lung assessment is indicated, in particular for mechanically ventilated patients. [expert consensus]  |
| <b>Examination technique</b>   |
| 1.3.5. The recommended method is bedside chest X-ray. In the vast majority of cases, this method is sufficient for assessing the patient's condition and helps avoid transporting the patient around the hospital. The recommended location of the mobile device is the ward where patients with COVID-19 are hospitalised. [expert consensus] |

### **Justification:**

Due to the risk of spreading the virus when transporting the patient for diagnostic tests, the American College of Radiology recommends considering the use of mobile/bedside apparatuses to minimise the risk of spreading the infection. The use of chest X-ray for early detection of lung disease may also play a role in the case of limited access to reliable rRT-PCR tests<sup>88</sup>.

The recommendation was based on the assessment of scarce scientific evidence combined with the consensus of a multidisciplinary panel of experts.

### **Chest CT scan**

|  |
|--|
| <b>Recommendations</b>   |
| <b>Indications</b>   |
| 1.3.6. No imaging tests are necessary in asymptomatic cases or in the case of mild upper respiratory tract symptoms (fever, cough, mild dyspnoea). [expert consensus]  |
| 1.3.7. Before deciding to refer a COVID-19 patient for a CT scan, both the benefits and inconveniences associated with this test should be taken into account (including patient transport, the need to secure the transport route, decontamination of the CT scanner, and making the CT scanner temporarily unavailable to other patients). [expert consensus]  |
| 1.3.8. In the case of clinical indications for lung assessment (persistent cough and/or symptoms suggestive of lung involvement), a chest CT may be performed. Despite its non-specificity, CT imaging– along with comprehensive clinical evaluation– may be helpful in preliminary diagnosis of COVID-19. For a final diagnosis, a positive rRT-PCR test is required. [expert consensus]  |
| 1.3.9. In exceptional cases (e.g. extensive waiting time for the rRT-PCR test result, suspected false negative rRT-PCR result, clinical symptoms suggestive of COVID-19 – probable case), the practitioner, together with the radiologist, may consider performing a CT scan, as long as its result would affect the patient management. A positive rRT-PCR test result is required for a final diagnosis of COVID-19 to be possible. [expert consensus] |

|   |
|---|
| 1.3.10. In the symptomatic stage without respiratory failure (MEWS: score <3) and in the pre-ARDS stage (MEWS: score 3-4), CT is highly sensitive in detecting interstitial changes and assessing their dynamics. Furthermore, a CT scan performed along with the assessment of gas exchange rates has prognostic value. [expert consensus]   |
| 1.3.11. In critically ill patients with acute respiratory distress syndrome (ARDS), impairment of other vital functions (hypotension, shock, multiple organ failure) and in mechanically ventilated patients, bedside X-ray is the preferred method of lung imaging. In justified cases requiring CT diagnostics, the patient should be ventilated using a transport ventilator. [expert consensus] |
| 1.3.12. A CT scan is also indicated in COVID-19 patients in whom complications, such as empyema or pulmonary abscess, or coexistence of other conditions, such as pulmonary embolism, are suspected. [expert consensus]   |
| <b>Examination technique</b>  |
| 1.3.13. Normally, chest CT in patients with suspected or confirmed COVID-19 is performed without intravenous administration of a contrast agent. [expert consensus]   |
| 1.3.14. High-resolution CT (HRCT) is the recommended technique. [expert consensus]  |
| 1.3.15. Contrast-enhanced CT is performed only when comorbidities, e.g. pulmonary embolism, are suspected. [expert consensus]   |

### **Justification:**

CDC guidelines do not recommend performing X-ray and CT scans to diagnose COVID-19, as the available evidence is inconsistent and inconclusive. In view of the above, the recommendations were based on the assessment of the compiled scientific evidence combined with the consensus of a multidisciplinary panel of experts.

In the initial period (about 2 days) of the COVID-19 infection, a CT scan may not show any lesions<sup>89,90</sup>. Although CT scans are characterised by high sensitivity in detecting lesions in the lungs, their specificity is low - other types of pneumonia give the same or similar images to COVID-19, i.e. pneumonia caused by other viruses, PCP (caused by *Pneumocystis jiroveci*), cryptogenic organising pneumonia (COP), acute lung damage due to toxic effects of drugs, hypersensitivity or autoimmune diseases<sup>91</sup>. In a Chinese study which included 1,014 patients in Wuhan, the CT image was indicative of pneumonia in 97% patients with positive rRT-PCR results, which suggests high sensitivity of CT<sup>92</sup>. However, another study, which included 104 patients from a cruise ship, diagnosed the presence of lesions in the lung parenchyma in 61% of patients with rRT-PCR-confirmed COVID-19, 79% in symptomatic patients, 54% asymptomatic patients.<sup>93</sup> Another retrospective study performed on 81 hospitalised patients indicated that COVID-19-associated pneumonia manifests as abnormalities in the chest CT scan even in asymptomatic patients, and opacity progresses rapidly and develops within 1-3 weeks. The authors conclude that combining imaging with a clinical assessment and laboratory results can facilitate early diagnosis of COVID-19 pneumonia<sup>94</sup>.

The testing technique depends on the apparatus and protocols used in a given centre.

### **Lung and pleural ultrasound**

Ultrasound is a recognised method of examining lungs and pleura, which is used in the diagnostics of both acute and chronic diseases affecting these organs<sup>95,96</sup>, therefore, it can also constitute a valuable element of clinical bedside analysis in patients with SARS-CoV-2<sup>97,98,99,100,101,102</sup>.

## Role of ultrasound in diagnosing and monitoring of COVID-19 patients

| <b>Recommendation</b>  |
|--|
| 1.3.16. Ultrasound assessment of the lungs and interpretation of ultrasound images require appropriate training and experience. Therefore, in COVID-19 patients, lung and pleural ultrasound should only be performed by doctors who have prior experience in the examination technique and interpretation of ultrasound images. Using ultrasound in the diagnosis of COVID-19 patients by clinicians and radiologists who do not have adequate experience in chest ultrasound or the ability to efficiently conduct the test according to recognised protocols is not recommended. [expert consensus] |
| 1.3.17. Lung and pleural ultrasound can be used at various stages of managing COVID-19 patients. They include:<br>a) triage <sup>103,104,105</sup> ,<br>b) monitoring the course of the disease and treatment <sup>106,107,108</sup> , also as a guide to make decisions about: <ul style="list-style-type: none"><li>• the use of prone position<sup>109</sup>,</li><li>• PEEP values<sup>110</sup>,</li><li>• fluid supply and the volume of diuresis<sup>111</sup>.</li></ul> [moderate strength of recommendation]   |

### **Justification:**

Severe COVID-19 pneumonia presents a similar clinical and radiological presentation as ARDS, and ultrasound images in patients with ARDS have already been well characterised<sup>112,113,114,115</sup>. Experience to date indicates that the lesions in the ultrasound image observed in COVID-19 pneumonia are quite characteristic (however not specific), and their extent and nature correlate with the patient's clinical condition<sup>116,117,118</sup>. It seems that patients with well-aerated front lung parenchyma and atelectasis in dorsal lung areas may particularly benefit from the use of prone position<sup>119</sup>. Similarly, the presence of disseminated B-lines may indicate the need of increasing PEEP<sup>120,121</sup>. The use of lung ultrasound in the assessment of the haemodynamic status, and as a helpful indicator in determining fluid supply, is already well documented<sup>122,123</sup>.

### **Advantages of lung and pleural ultrasound in COVID-19 patients**

Lung and pleural ultrasound is a fast, cheap and repeatable method<sup>124,125,126</sup>. It can be performed as a bedside procedure, thus reducing the number of X-ray and CT examinations which require transporting the patient to a relevant laboratory<sup>127,128</sup>. It can be performed by one person, which reduces the number of staff exposed to direct contact with the patient and allows for decreased use of personal protective equipment<sup>129</sup>. Results from different periods can be easily compared.<sup>130,131</sup>

### **Limitations of lung and pleural ultrasound in COVID-19 patients**

The main limitation of ultrasound in the COVID-19 diagnostics is the low specificity of the identified lesions. A presentation similar to the one described above, or some of its elements, may accompany other lung diseases including pulmonary fibrosis<sup>132,133</sup>, viral pneumonia of another aetiology<sup>134</sup>, pulmonary oedema<sup>135</sup>, bacterial pneumonia<sup>136</sup>. Another limitation of the study is the inability to visualise the centrally located (perihilar) lesions<sup>137</sup>.

## 1.4. Bronchoscopy

| <b>Recommendation</b> |   |
|-----------------------|---|
| 1.4.1.                | Bronchoscopy, performed to collect diagnostic samples (BALF, brush biopsy) can be used only in exceptional cases and when relevant conditions are met (including other situations where a bronchoscopy is absolutely indicated, the need for tests for another aetiology of pneumonia, cases of mechanically intubated and ventilated patients, providing healthcare professionals with full personal protective equipment) [moderate strength of recommendation] |
| 1.4.2.                | If diagnostic bronchoscopy is performed in COVID-19 patients, the minimum volume of fluid to be collected from the lower respiratory tract should be 2-3 mL <sup>138</sup> [expert consensus]   |
| 1.4.3.                | If available, single-use bronchoscopes are recommended for performing bronchoscopy in patients with COVID-19 <sup>139,140</sup> . [expert consensus]  |
| 1.4.4.                | The facility performing bronchoscopy in patients with COVID-19 must have developed and tested procedures for disinfecting reusable equipment and apparatus <sup>141,142</sup> [expert consensus]  |

### **Justification:**

Due to the high risk of transmitting infected aerosol, as well as the risk of aggravating hypoxemia, bronchoscopy is not routinely used in the diagnosis of COVID-19.<sup>143,144,145</sup>

## 2. TREATMENT

### 2.1. Pharmacotherapy

#### 2.1.1. Analysis of drugs used in COVID-19

*The Steering Committee decided to conduct an analysis of primary studies concerning the use of selected drugs and medicinal products promoted / indicated as effective against COVID-19. In the first stage of works on the Recommendations, the focus has been on a limited number of these drugs, and in the further work the list will be expanded and new scientific data on the drugs already analysed will be taken into account when revising the current records. Primary studies have been identified and analysed by the AOTMiT Analysts.*

#### **Remarks of the AOTMiT**

*The AOTMiT analysts have conducted a systematic search of medical information databases in order to find therapeutic treatment guidelines in COVID-19 and primary scientific reports for identified drugs with therapeutic potential (the search was performed using PubMed (via Medline) and EMBASE databases; the last update was carried out on 21 April 2020. Websites of scientific journals, as well as pre-print reports, available at <https://www.medrxiv.org/>, were also viewed complementary to the search. A list of the analysed drugs is attached (Annex no. 1).*

*Below we present critical evaluations of primary studies which constitute the basis for drawing conclusions on the efficacy of the analysed therapeutic interventions.*

*Currently, off-label use of medicinal products or using medicinal products without marketing authorisation in treatment of COVID-19 patients should only take place in hospitals. All possible adverse effects should be considered and appropriate precautions must be taken. Since the efficacy and safety profiles of the applied drugs are unknown, patients should always be informed accordingly about the uncertain efficacy and toxicity of the drugs and, if their condition allows it, should consent to their administration (in line with applicable legislation). It is also possible to use other drugs with a potential antiviral effect and a proven safety profile (at least phase 2 clinical trial or a medical experiment with a drug used in another indication).*

*The use of drugs must not have an adverse impact on the organisation of optimal symptomatic care, which still offers the highest probability of a favourable disease course. Furthermore, patients are entitled to pain management in line with current medical knowledge.*

### 2.1.1.1. Heparins

| <b>Recommendation</b>   |
|---|
| Routine use of low-molecular-weight heparins in prophylactic doses in severe COVID-19 patients is recommended due to the frequent occurrence of deep vein thrombosis and pulmonary embolism risk factors. |

**Justification:**

Prophylaxis, which reduces the risk of deep vein thrombosis and pulmonary embolism in at-risk patients, has a well-established position in the scientific literature and a series of Polish and foreign clinical guidelines. Patients with a severe infection, lesions in the lungs, fever, breathing with dry gases, e.g. oxygen, with limited mobility, are subject to an increased risk of thrombosis. Treatment of these patients is comprehensively described in Polish and foreign guidelines and in basic manuals such as Interna Szczeklika.

With specific regard to patients with COVID-19, the International Society on Thrombosis and Haemostasis recommends that all patients hospitalised in connection with this disease, particularly those in the Intensive Care Unit, should receive prophylactic doses of low-molecular-weight heparins unless there are contraindications for such treatment (bleeding or the amount of platelets  $< 25 \times 10^9/L$ )<sup>146</sup>. In case of contraindications for the use of heparins, mechanical methods such as intermittent compression of the lower limbs with pneumatic cuffs should be considered.

UK recommendations<sup>147</sup> also recommend prophylaxis of venous thromboembolism for all high-risk patients and considering the likelihood of pulmonary embolism in patients with sudden deterioration of oxygen saturation, respiratory failure and reduced blood pressure.

The use of low-molecular-weight heparins rather than oral anticoagulants is recommended, including a change of therapy to heparins in patients who have received direct oral anticoagulants (DOAC) or vitamin K antagonists.

Concerning the use of heparin in COVID-19, 3 retrospective studies (Tang 2020, Chen Shi 2020 and Zhang 2020) were identified. The results of the first two studies are presented in the following tables.

**Table 4. Description of the methodology and results of Tang 2020 – heparins**

| Tang 2020 <sup>148</sup>   |  |                  |   |  |   |               |   |
|--|--|------------------|---|--|---|---------------|---|
| Study methodology  | Population / endpoint  | Observation time | Intervention  | Control  | Relative parameter (95% CI), p value  | NNT (95% CI)* | Clinical relevance                                  |
| <b>Retrospective</b><br>single-centre analysis (Wuhan, China)<br>Of the 1,786 patients admitted to the hospital, 449 had a severe course of the disease and met the inclusion criteria.<br>The patients were stratified according to the SIC (sepsis induced coagulopathy) scale score and D-dimer concentration.<br>Treatment: from 01/01/2020 to 13/02/2020, 28-day-long observation   | N=449<br>Average age: 65.1 ± 12.0 y.o.<br>Men: 59.69 %<br>Co-morbidities 60.6%<br>Meeting the SIC criteria: 21.6%<br><br>Inclusion criteria: COVID-19 patients in severe condition, i.e. with tachypnoea at >30/min; saturation at < 93% at rest; PaO <sub>2</sub> / FiO <sub>2</sub> ≤300 mmHg.<br>Exclusion criteria: haemorrhagic disorder; hospital stay < 7 days; no coagulation parameters or anticoagulant drugs; age < 18 y.o. |                  | Ni=99 including n=94 enoxaparin 40-60 mg/day<br>• UFH, n=5 unfractionated, 10-15,000 units/day<br>+ Antiviral and standard therapy. | Nk=350<br>no use or use of heparins for less than 7 days<br>+ antiviral and standard therapy | Current clinical practice in Poland. In all severe conditions, especially in case of immobilisation, high fever, intensive therapy, unless there are any contraindications, in particular haemorrhagic ones, venous thromboembolism prophylaxis with the use of heparins, especially low-molecular-weight heparins, is applied. |               |   |
| Limitations: patients in the control arm could use heparins, although for a shorter period of time; no standard therapy was specified  | 28-day mortality rate  | 28 days          | (30/99)<br>30.3%  | (104/350)<br>29.7%   | NDA, p=0,910  |               |   |
|  | 28-day mortality rate, patients in the SIC scale ≥ 4 (n=97)  | 28 days          | 40.0%   | 64.2%,   | OR=0.372 (0.154; 0.90), p=0.029   | 5* (3; 10)    | Clinically significant endpoint, significant result |
|  | 28-day mortality rate, patients in the SIC scale ≤ 4 (n=352)   | 28 days          | 29.0%   | 22.6%  | OR=1.284 (0.700-2.358)  | ND            |   |
|  | 28-day mortality rate, patients with D-dimer > 6x upper limit of norm (n=161)  | 28 days          | 32.8%   | 52.4%,   | OR=0.442 (0.226; 0.865), p=0.017  | 6* (4;11)     | Clinically significant endpoint, SI                 |
| <b>Conclusions: A retrospective observational study on the use of heparins, including mainly low-molecular-weight heparin ranging from a prophylactic dose to half dose in severe patients with a COVID-19 infection. The control arm were patients who did not receive heparins or used them only shortly. The study demonstrated a statistically significant and clinically relevant difference in the case of patients with a &gt;4 SIG score. The study indicates the importance of using the SIG scale (scale of coagulopathy provoked by sepsis) and D-dimer levels. Although the results are very interesting, they require further verification tests.</b> |  |                  |   |  |   |               |   |

Detailed results obtained for patients stratified to different levels of D-dimer are available in the source publication.

\* - the Agency's own calculations; N/A – for statistically insignificant differences in RR, no absolute parameter values were estimated (NNT/NNH)

A chart showing the dependence of 28-day mortality from scores on the SIC coagulopathy scale and the D-dimer level available in Tang 2020 is presented in the annex (Annex no. 2).

**Table 5. Description of the methodology and results of Chen Shi – heparins**

| Chen Shi 2020 <sup>149</sup>   |   |                  |   |   |   |              |                      |
|--|---|------------------|---|---|---|--------------|----------------------|
| Study methodology  | Population / endpoint   | Observation time | Intervention  | Control   | Relative parameter (95% CI), p value  | NNT (95% CI) | Clinical relevance   |
| Retrospective single-centre analysis (Wuhan, China)<br>Study: 1.02. – 15/03/2020   | N=42<br>Age (average): 69 years<br>Men: 62 %  |                  | N=21<br>Dosage:<br>Enoxaparin 4000 IU 1x per day i.h.<br>Nadroparin 4100 IU 1x per day i.h.<br>LMWH 5000 IU 1x per day i.h  | N=21<br>Antiviral treatment and supportive care including:<br>- Arbidol<br>- Interferon alfa-2B<br>- Traditional Chinese medicine | Current clinical practice in Poland.<br>In all severe conditions, especially in case of immobilisation, high fever, intensive therapy, venous thromboembolism prophylaxis with the use of heparins, especially low-molecular-weight heparins, is applied unless there are any contraindications, in particular haemorrhagic ones. |              |                      |
|  | Inclusion criteria: pneumonia caused by SARS-CoV-2 + at least one: dyspnoea; tachypnoea ≥30/min; saturation at 93% at rest; PaO2/FiO2 ≤300 mmHg; lesions in the lung image progressing by > 50% within 24-48h classified as severe; age ≥ 18 y.o.; no previous lung diseases; no immunosuppression, glucocorticosteroids.<br>Exclusion criteria: severe systemic diseases or other acute or chronic infectious diseases; liver, kidney or congenital heart defects; previous therapy with low-molecular-weight heparin; mental illness; critical condition of the patient in the ICU; contraindications or allergy to heparins.   |                  | Antiviral treatment and supportive care depending on the patient including:<br>- Arbidol<br>- Interferon alfa-2B<br>- Ribavirin<br>- Lopinavir/ritonavir<br>- Traditional drugs of Chinese medicine |   |   |              |                      |
| Limitations: small population; single centre   | Number of days to negative test result for the virus presence   | NDA              | 20 (IQW 11-31)  | 19 (IQW 12-30)  | N/A, p=0.46   | N/A          | No major differences |
|  | Duration of hospitalisation [days]  | NDA              | 29 (IQW 17-42)  | 27 (IQW 24-31)  | N/A, p=0.41   | N/A          |                      |
|  | The authors also analysed laboratory parameters related to the development of inflammation in patients. The percentage of lymphocytes increased in the heparin arm; according to the authors, this may suggest its potential anti-inflammatory effect. The number of platelets also increased in the heparin arm compared to the control arm. No differences were observed between the arms with regard to RBC, WBC, % neutrophils and % monocytes. Of the proinflammatory cytokines analysed by the authors, interleukin 6 was observed to decrease concentration of in the group of patients treated with LMWH. The authors of the study suggest that the potential anti-inflammatory effects of heparins may therefore be related to the reduction of Il-6 levels. |                  |   |   |   |              |                      |
| Conclusions: A retrospective analysis of a small study arm does not provide relevant scientific evidence and does not change the indications for the use of prophylactic low-molecular-weight heparins to reduce the risk of deep vein thrombosis and pulmonary embolism. It suggests that perhaps the use of low-molecular-weight heparins has a positive effect on lymphocyte and IL-6 levels. |   |                  |   |   |   |              |                      |

N/A – for statistically insignificant differences in RR, no absolute parameter values were estimated (NNT/NNH); NS – statistically insignificant differences; NDA – no data available

Zhang 2020 assesses the coagulation profile and clinical status of patients with severe COVID-19 in the intensive care unit. In this retrospective analysis, 7 patients with peripheral ischaemia and cyanosis (acro-ischaemia) in critical condition were included. The median age of patients was 59 years, four patients were male. Typical symptoms in patients were fever, cough, dyspnoea and diarrhoea. All patients had symptoms of peripheral ischaemia with cyanosis of fingers and skin lesions, including dry

necrosis. In most cases, the level of D-dimer and FDP (fibrinogen degradation products) was significantly increased. Prothrombin time was extended in 4 patients. D-dimer and FDP levels increased as COVID-19 exacerbated. 4 patients were diagnosed with DIC syndrome (disseminated intravascular coagulation). 6 patients were treated with low-molecular-weight heparins, followed by a decrease in D-dimer and FDP levels, however no improvement in their clinical status was observed. 5 patients died and the median time from the occurrence of acro-ischaemia to death was 12 days. Perhaps using low-molecular-weight heparin at an earlier stage would have provided a better final result.

In another publication entitled *Coagulopathy and Antiphospholipid Antibodies in Patients with COVID-19*, Zhang et al. described three patients with a severe coronavirus infection in whom coagulation disorders were caused by antiphospholipid syndrome (APS). The differences in treatment in these coagulopathies suggest the need to control whether coagulation disorders are not associated with the release of antiphospholipid antibodies caused by infection, which generates a strong coagulation tendency. In such cases, low-molecular-weight heparins are used in therapeutic doses (e.g. enoxaparin 1mg/kg of weight s.c. twice a day). Heparins play an additional role, as they not only inhibit the coagulation cascade by influencing the Xa factor and thrombin, but also hamper the effect antibodies have on phospholipids, thus reducing the stimulation of inflammation and thrombosis. The authors described patients with COVID-19 with catastrophic antiphospholipid syndrome (CAPS) in which thrombosis in small arterial vessels (stroke, arterial embolism, distal limb ischaemia) is observed. In APS, antiplatelet drugs are used along with heparins (aspirin 75mg, clopidogrel 75mg, sometimes both combined). One of the drugs with antithrombotic effects used in APS is hydroxychloroquine (HQC) – this is interesting because the results of COVID-19 treatment have been identified to suggest the effectiveness of HQC (for more see the HQC analysis). The above-mentioned report and observations of frequent coagulation disorders in COVID-19 suggest that there is risk of the antiphospholipid syndrome.

|                       |
|-----------------------|
| <b>Recommendation</b> |
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| The use of low-molecular-weight heparins in COVID-19 is not limited to antithrombotic prophylaxis – therapeutic doses should be used in thrombosis, while antiplatelet drugs, hydroxychloroquine and a statin should be additionally used in the antiphospholipid syndrome. |
|---|

The use of low-molecular-weight heparin is associated with an increased risk of bleeding. The group of patients requiring special precautions are patients with renal impairment (who should use unfractionated heparin rather than low-molecular-weight heparin), low body weight, obese and elderly patients.

### 2.1.1.2. Convalescent plasma

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|-----------------------|
| <b>Recommendation</b> |
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| In the absence of confirmed efficacy data, routine use of convalescent plasma is not recommended; its use should be restricted to clinical trials. |
|--|

Four case series (Duan 2020, Schen 2020, Zhang 2020 and Ahn 2020) regarding the efficacy and safety of convalescent plasma in COVID-19 have been identified –

**Table 6. Description of the methodology and results of the studies which assessed the efficacy and safety of convalescent plasma**

| Study                        | Duan 2020 <sup>150</sup>  | Schen 2020 <sup>151</sup>   | Zhang 2020 <sup>152</sup>   | Ahn 2020 <sup>153</sup>  |
|------------------------------|---|---|---|--|
| <b>Methodology</b>           | Series of cases between 23/01/2020 and 19/02/2020 in three Chinese hospitals  | Description of a series of cases between 20 January and 25 March 2020   | Case series description   | Two case studies   |
| <b>Population</b>            | 10 patients with COVID-19 (rRT-PCR-confirmed) in severe condition<br>Inclusion criteria: age $\geq$ 18 years, respiratory failure with tachypnoea at $>30$ /min or saturation at $< 93\%$ at rest or $PaO_2 / FiO_2 \leq 300$ mmHg.<br>Exclusion criteria: allergy to plasma or its ingredients (sodium citrate), serious general conditions which exclude the possibility of CP transfusion. | - 5 patients with confirmed COVID-19 and acute respiratory distress syndrome (ARDS)<br>Inclusion criteria: severe, rapidly progressive pneumonia; consistently high viral load in the blood despite antiviral treatment, $PAO_2 / FIO_2 < 300$ mmHg, mechanical ventilation.  | 4 patients with confirmed COVID-19 in critical condition; including: 3 patients between 55 and 73 years of age and one 31-year-old pregnant patient | Patient 1: man, 71 years old, no comorbidities;<br>Patient 2: woman, 67 years old, with hypertension   |
| <b>Intervention</b>          | - One dose of 200 mL CP with antibody titres above 1:640<br>- CP was used as a supplement to the best supportive and antiviral treatment<br>- Plasma donors: 10 recovered COVID-19 patients* (the donor's blood was collected 3 weeks after onset and 4 days after discharge)   | <b>Two doses of plasma</b> , with the volume of 200-250 mL each (in total, each patient received 400 mL of plasma) with specific antibody concentration measured using the ELISA method, greater than 1:1,000.<br>CP therapy has been used as a supplement to antiviral and standard treatment.<br>Plasma donors:<br>- 5 patients aged 18 to 60<br>- All donors had been previously diagnosed with laboratory-confirmed COVID-19, and have been healthy (asymptomatic) for at least 10 days.<br>- During blood donation, everyone was tested for SARS- CoV-2 and other respiratory viruses, as well as hepatitis B, hepatitis C, HIV and syphilis.<br>- Plasma was administered to the recipients immediately, on the same day on which it was collected.<br>- All patients were mechanically ventilated and all patients received antiviral and methylprednisolone treatment | Due to deteriorating clinical condition and symptoms of acute respiratory failure, a decision on administering convalescent plasma was made.        | <b>Patient 1</b><br>After 12 days of persistent cough and fever, the patient was admitted to the clinic – positive rRT-PCR for COVID-19<br>After admission to the hospital, hydroxychloroquine therapy was initiated: 400 mg/day.<br><b>Day 2</b> of hospitalisation – X-ray examination, benign changes in the lower right lung field – lopinavir/ritonavir, 400 mg/100mg, 2 per day, was added to hydroxychloroquine.<br>On <b>day 3</b> , increased oxygen demand – transfer to a higher-reference level hospital<br>On admission: no subjective dyspnoea with oxygen flowing through a nasal cannula at 4L/min, respiration rate $>30$ x/min.; X-ray examination – rapid increase of bilateral infiltrates; blood tests: white blood cell count (WBC): $3.53 \times 10^3/\mu\text{L}$ with lymphopaenia: $0.4 \times 10^3/\mu\text{L}$ ; C-reactive protein (CRP): 59.7 mg/L; lactate dehydrogenase (LDH): 814 IU/L; interleukin 6 (IL-6) 101.3 pg/mL.<br>intubated patient, initiation of mechanical ventilation (in line with the ARDS procedure guidelines).<br>Despite continuing pharmacotherapy, fever and deterioration of imaging results occurred. Blood tests: Increased CRP (172.6 mg/L), increased IL-6 (208.2 pg/mL).<br><b>day 9</b> – $PaO_2/FiO_2$ arterial blood gas analysis = 86 (severe ARDS), intravenous administration of methylprednisolone, 1 mg/kg/day, 1 per day.<br><b>day 10</b> – 500 mL of plasma was collected from a cured male patient (21 days without COVID-19). Anti-SARS-CoV-2 level – optical density ratio (OD) for IgG = 0.586 (limit value: 0.22). Plasma was administered in 2 doses, at 12-hour intervals (each dose was administered for 1 hour). No adverse reactions were observed following plasma administration. |
| <b>Endpoints and results</b> | - Primary endpoint: safety of CP transfusion<br>- Secondary endpoint: improvement of clinical symptoms and laboratory parameters within 3 days after CP transfusion.  | Endpoints:<br>- change in body temperature,<br>- assessment of organ failure associated with sepsis on the SOFA scale (range 0-24, with higher results indicating a more severe disease)  | - Clinical improvement was reported in all patients.<br>- 3 patients were discharged.   |  |

| Study              | Duan 2020 <sup>150</sup>  | Schen 2020 <sup>151</sup>  | Zhang 2020 <sup>152</sup>   | Ahn 2020 <sup>153</sup>  |
|--------------------|---|--|---|--|
|                    | <p><b>RESULTS:</b></p> <ul style="list-style-type: none"> <li>- The level of immune antibodies increased sharply to 1:640 in 5 cases, the other 4 remained high (1:640). The antibody levels were not measured in 1 patient.</li> <li>- With increased oxyhaemoglobin saturation in the blood, the clinical symptoms, in particular fever, cough, dyspnoea and chest pain, improved significantly or disappeared completely within 3 days. Some parameters improved compared to pre-transfusion results; increased lymphocyte count (<math>0.65 \times 10^9/L</math> vs <math>0.76 \times 10^9/L</math>) and decreased C-reactive protein (55.98 mg/L vs 18.13 mg/L).</li> <li>- Radiological studies have shown a different degree of regression of lung lesions over 7 days.</li> <li>- The viral load was undetectable after transfusion in seven patients with pre-existing viraemia. No serious adverse events were observed.</li> </ul> | <ul style="list-style-type: none"> <li>- PAO<sub>2</sub> / FIO<sub>2</sub>,</li> <li>- viral load,</li> <li>- serum antibody titre,</li> <li>- biochemical blood test results,</li> <li>- ARDS,</li> <li>- extracorporeal membrane oxygenation (ECMO) before and after plasma transfusion.</li> </ul> <p><b>RESULTS:</b></p> <ul style="list-style-type: none"> <li>- Within 3 days from plasma transfusion, 4 patients had normalised body temperature, lower SOFA scores, and their PAO<sub>2</sub>/FIO<sub>2</sub> value increased within 12 days (range: 172-276 before and 284-366 after transfusion). A decrease in SARS-CoV-2 in the viral load was also observed, and it was undetectable 12 days after transfusion, while the level of immune antibodies in the blood increased.</li> <li>- In 4 patients, the acute respiratory distress syndrome resolved on day 12 after transfusion. 3 patients were discontinued from mechanical ventilation within 2 weeks of treatment.</li> <li>- 3 out of 5 patients were discharged from the hospital (length of stay: 53, 51 and 55 days) and 2 are stable (37 days after transfusion).</li> </ul> | <ul style="list-style-type: none"> <li>- 1 patient was transferred from the intensive care unit due to the observed improvement.</li> <li>- The time until tested negative for the virus (rRT-PCR test) was 3 to 27 days from the time of the first transfusion.</li> <li>- No serious adverse events were observed.</li> </ul> | <p>On <b>day 11</b>, decrease in fever, decrease in oxygen demand; improved condition of the patient; CRP and IL-6 decreased to the reference range (5.7. mg/L and &lt;1.5 pg/mL, respectively).<br/>On <b>day 18</b>, PaO<sub>2</sub>/FiO<sub>2</sub> = 300.<br/>Negative SARS-CoV-2 test result after <b>26 days</b>.</p> <p><b>Patient 2</b></p> <p>Symptoms: fever, myalgia – positive rRT-PCR for COVID-19, hospitalised on the next day.<br/>After the start of hospitalisation, hydroxychloroquine therapy 400 mg/day + lopinavir/ritonavir 400 mg/100 mg, 2 per day + empiric antibiotic therapy increased oxygen demand; deteriorating infiltrates in the lower left lung field – on <b>day 3</b>, transfer to a hospital with a higher reference level. 93% of saturation with oxygen flow at 4 L/min through a nasal cannula at 24x/min; blood test results: mild leukocytosis (<math>12.67 \times 10^3 / \mu L</math>) with lymphopaenia (<math>0.7 \times 10^3 / \mu L</math>), increased CRP, increased IL-6 and increased LDH (respectively: 131.1 mg/L, 474.7 pg/mL, 344 IU/L).</p> <p>Despite the use of oxygen therapy with high oxygen flow, deterioration of bilateral infiltrates of the lungs and hypoxia – intubated on day 4, start of mechanical ventilation; intravenous administration of methylprednisolone at 0.5 mg/kg/day 1 per day.<br/>High fever; increased CRP (314 m/L), increased WBC (<math>21.79 \times 10^3/\mu L</math>), lymphopaenia (<math>0.5 \times 10^3 / \mu L</math>), PaO<sub>2</sub>/FiO<sub>2</sub> = 76 (severe ARDS). Chest X-rays and oxygen demand improved after including steroids and putting the patient in the face-down position (in line with the ARDS procedure guidelines)</p> <p><b>Day 6</b> – plasma was collected from a cured male patient (18 days without COVID-19, OD for IgG was 0.532.<br/>Plasma was administered as in the case of the first patient. No adverse reactions were observed following plasma administration. Leukocytosis and lymphopaenia resolved immediately after plasma administration.<br/>On <b>day 9</b> – X-ray: improvement of bilateral infiltrate density, PaO<sub>2</sub>/FiO<sub>2</sub> = 230; CRP and IL-6 – return to the reference values.<br/>Negative SARS-CoV-2 test result after <b>20 days</b>.<br/>The patient was successfully extubated and discharged on <b>day 24</b>.</p> |
| <b>Limitations</b> | <ul style="list-style-type: none"> <li>- In addition to plasma transfusions, patients simultaneously received standard treatment.</li> <li>- All study participants used antiviral therapy and, as a result, it cannot be excluded that the antiviral agents may have contributed to the patients'</li> </ul>   | <ul style="list-style-type: none"> <li>- Several uncontrolled case studies. It is unclear whether the patients' condition would have improved without plasma transfusions, as the patients received also other treatments (including antiviral treatment).</li> </ul>  | <ul style="list-style-type: none"> <li>- Descriptive nature of the study,</li> <li>- Small sample size;</li> <li>- Varied course of therapy</li> </ul>  | <ul style="list-style-type: none"> <li>- The number of antibodies in the plasma administered to the patients who not been standardised.</li> <li>- Plasma was administered with antiviral drugs, steroids, hydroxychloroquine and antibiotics, which may affect the relationship between plasma and the patient's antibody level, distorting the results.</li> </ul>   |

| Study              | Duan 2020 <sup>150</sup>   | Schen 2020 <sup>151</sup>  | Zhang 2020 <sup>152</sup>  | Ahn 2020 <sup>153</sup>   |
|--------------------|--|--|--|---|
|                    | <p>recovery or synergised with the therapeutic effects of CP.</p> <ul style="list-style-type: none"> <li>- Some patients received glucocorticoid therapy, which may interfere with the immune response and delay the removal of the viral load from the blood.</li> <li>- The median time from the onset of symptoms to CP transfusion was 16.5 days (IQR: 11.0–19.3 days).</li> <li>- Although viraemic kinetics during natural history remains unclear, the relationship between the reduction of SARS-CoV-2 RNA and CP therapy, as well as optimal concentration of neutralising antibodies and treatment schedule, should be further clarified.</li> </ul> | <ul style="list-style-type: none"> <li>- It is not possible to establish whether the observed health improvement is related to plasma administration or the pharmacotherapy used.</li> <li>- Plasma transfusions were carried out within 10 to 22 days from admission; however, it is not possible to determine whether the duration of treatment affects the final results.</li> <li>- The treatment's effect on mortality is not known.</li> </ul> |  |   |
| <b>Conclusions</b> | <p>A pilot study on CP therapy showed a potential therapeutic effect and a favourable safety profile in the treatment of COVID-19 patients in severe condition. One dose of CP with a high concentration of neutralising antibodies can quickly reduce the viral load and improve clinical parameters. The optimal plasma dose and administration moment (time from the onset of the symptoms), as well as the clinical benefits of the CP, require further studies in larger, controlled trials.</p>  | <p>The authors of the publication stated that the above results may suggest the efficacy of blood transfusions in the treatment of COVID-19 with ARDS, although the limited sample size and study design exclude the possibility of drawing final conclusions on the efficacy of the analysed treatment, therefore randomised clinical trials are required to fully assess the effect of the therapy.</p>  | <p>Plasma may be efficacious in the treatment of severe COVID-19 cases, but it requires further investigation.</p> | <p>According to the authors, the case studies may suggest that the use of plasma collected from patients who recovered from COVID-19 should be treated as an additional treatment option, without causing serious adverse effects. They also indicate that, when used with systemic corticosteroids, one can expect a reduction in the excessive inflammatory response caused by corticosteroids, while also reducing the viral load by the plasma. However, they emphasise that further well-designed trials are necessary to demonstrate the efficacy and safety of plasma transfusions in patients with COVID-19, as the results of currently available evidence are not representative of the entire target population.</p> |

\* Recovery was defined as: body temperature within the normal range for more than 3 days, resolution of respiratory symptoms and two consecutive negative SARS-CoV-2 results obtained from a sputum sample in the rRT-PCR test (single-day interval sampling)

**Table 7. Description of the methodology and results of Liu 2020 – convalescent plasma**

| Liu 2020  |  |   |   |               |  |  |              |                    |    |
|---|--|---|---|---------------|--|--|--------------|--------------------|----|
| Convalescent plasma treatment of severe COVID-19: A matched control study   |  |   |   |               |  |  |              |                    |    |
| Methodology   | Population   | Intervention  | Control   |               | Standard clinical practice                                     | Limitations  |              |                    |    |
|   |  |   | 1:4   | 1:2           |  |  |              |                    |    |
| Experimental study with retrospectively matched control arms (1: 4/1:2 match),<br>Hospitalisation time: 24/03/2020-08/04/2020<br><br>Country: United States   | COVID-19 patients<br><br>Average age: 55 (± 13) years<br>men: 64%<br>obesity (BMI≥30): 54%<br>smoking (currently or in the past): 18%<br><br>On the day of transfusion:<br>Oxygen therapy: 87%<br>Mechanical ventilation: 10%<br>Retrospectively matched control group – patients hospitalised in the same period (standardised average difference in predictive factors between the study arm and control arm: <0.2). | Ni=39 convalescent plasma<br><br>2 CP units (approx. 250 mL, infusion time: 1-2 h);<br>Monitoring for indications for oxygen therapy: on days 1, 7 and 14 after transfusion: 69.2% – high-flow oxygen, 10.3% – mechanical ventilation | Nk1=156<br>BSC  | Nk2=74<br>BSC | in Poland – no established COVID-19 procedure                  | <ul style="list-style-type: none"><li>Retrospective matching of control arms;</li><li>Lack of detailed baseline characteristics of patients in the control arms;</li><li>Patients in the study arms – high heterogeneity in relation to oxygen needs on the day of transfusion and duration of symptoms;</li><li>Cohort was too small to indicate differences in the analysis of subgroups other than intubated vs non-intubated patients;</li><li>Small subpopulation of intubated patients – inconclusive; need for further research;</li><li>Pre-print.</li></ul> |              |                    |    |
|   |  |   | The matching of the control arm took into account the characteristics of the patients in the study arm (pharmacotherapy, intubation and its duration, length of hospitalisation and oxygen needs) |               |  |  |              |                    |    |
|   |  |   | AZM (%)   | 79            |  |  |              | 85                 | 85 |
|   |  |   | HCQ (%)   | 92            |  |  |              | 95                 | 93 |
| Results   |  |   |   |               |  |  |              |                    |    |
| Endpoint  | Treatment period (days)  | Intervention  | Control   |               | Relative parameter (95% CI)                                    |  | NNT (95% CI) | Clinical relevance |    |
|   |  |   | 1:4   | 1:2           | 1:4  | 1:2  |              |                    |    |
| Discharge (%)   | To 01/05/2020  | 71.8  | 66.7  | 68.9          | Subpopulation of non-intubated patients: HR=0.19 (0.05-0.72)** |  |              |                    |    |
| Mortality (%)   |  | 12.8  | 24.4  | 21.6          | RR= 0.53 (0.22; 1.25)^   | RR= 0.59 (0.23; 1.5)^  |              |                    |    |
| Deterioration of respiratory function   | 14   | 18  | 24.3  |               | OR=0.86 (0.75: 0.98)*  |  |              |                    |    |
| Conclusions: Initial results indicate the benefit of plasma therapy in relation to overall survival of hospitalised COVID-19 patients. Data indicate the possibility of a therapeutic effect more than a week after the transfusion. At the same time, the results of the study suggest that non-intubated patients may benefit from CP therapy more than intubated patients. |  |   |   |               |  |  |              |                    |    |

^Agency's own calculations; \*covariates-adjusted analysis \*\*adjusted variables, Cox model

**Table 8. Description of the methodology and results of Jin 2020 – convalescent plasma**

| Study               | Jin 2020 <sup>154</sup>   |   |   |                           |                                   |  |  |
|---------------------|---|---|---|---------------------------|-----------------------------------|--|--|
|                     | Treatment of 6 COVID-19 Patients with Convalescent Plasma   |   |   |                           |                                   |  |  |
| <b>Methodology</b>  | <ul style="list-style-type: none"> <li>Case series – 6 patients</li> <li>Single-centre</li> <li>Observation time – hospitalisation time: 49-64 days</li> <li>Plasma donors: two subsequent negative test results and no symptoms for at least 3 weeks, serum antibody titre &gt;1:1,000, neutralising antibody titre &gt; 40</li> </ul>   |   |   |                           |                                   |  |  |
| <b>Population</b>   | <ul style="list-style-type: none"> <li>Previous treatment: antiviral drugs and corticosteroids</li> <li>Inclusion criteria: <ul style="list-style-type: none"> <li>COVID-19 confirmed with a RT-PCR test</li> <li>persistent positive SARS-CoV-2 and rapidly developing severe disease or</li> <li>recurrent patients and patients whose condition deteriorated after empiric antiviral treatment</li> </ul> </li> <li>Exclusion criteria: <ul style="list-style-type: none"> <li>patient allergic to plasma components</li> <li>positive HBV, HCV or HIV test result</li> <li>bacterial infection</li> </ul> </li> </ul> |   |   |                           |                                   |  |  |
|                     |   | <b>Patient 1</b>                            | <b>Patient 2</b>  | <b>Patient 3</b>          | <b>Patient 4</b>                  | <b>Patient 5</b>   | <b>Patient 6</b>   |
|                     | <b>Sex/age</b>  | F/64  | M/75  | M/64                      | M/51                              | F/53   | M/56   |
|                     | <b>Patient's condition</b>  | Serious critical                            | Serious critical  | Critical                  | general <sup>s</sup> (relapse)    | general <sup>s</sup> (relapse)   | Critical (relapse)   |
|                     | <b>Co-morbidities</b>   | myocardial ischemia, diabetes, stroke       | myocardial insufficiency, oesophageal cancer (after surgery)              | None                      | none                              | hypertension, hyperlipidaemia, diabetes, recovery from cholecystectomy, hysterectomy and tonsillectomy | hypertension, myocardial ischemia, stroke, bilateral renal artery stenosis |
|                     | <b>Complications prior to plasma transfusion</b>  | bacterial pneumonia, ARDS, moderate anaemia | bacterial and fungal pneumonia, ARDS, moderate anaemia, myocardial injury | bacterial pneumonia, ARDS | bacterial pneumonia, liver damage | none   | none   |
|                     | <b>Time from admission to CP transfusion</b>  | 22  | 30  | 38                        | 38                                | 63   | 64   |
| <b>Intervention</b> | <ul style="list-style-type: none"> <li>Convalescent plasma (unit volume: 200 mL); transfusion on the day of collection, between day 22 and 64 from admission; Patients 1 and 2 received 2 plasma units (the second unit was administered on the following day);</li> <li>Concomitant antiviral therapy + corticosteroids</li> </ul>   |   |   |                           |                                   |  |  |
|                     | After plasma transfusion, PaO2/FiO2 parameters and lymphocyte counts in Patients 1, 2 and 3 reached normal values.  |   |   |                           |                                   |  |  |

| Study  | Jin 2020 <sup>154</sup>  |        |                                 |                       |                    |                    |                               |           |
|--|--|--------|---------------------------------|-----------------------|--------------------|--------------------|-------------------------------|-----------|
|  | Treatment of 6 COVID-19 Patients with Convalescent Plasma  |        |                                 |                       |                    |                    |                               |           |
| Endpoints and results<br>Endpoints and results | The level of inflammatory CRP and IL-6 markers decreased significantly.<br>CT results showed a gradual regression of lung lesions.<br>Patients 4 and 6 were negative in two consecutive tests conducted after CP transfusion, on day 24 and day 3, respectively. |        |                                 |                       |                    |                    |                               |           |
|  | Parameter  | CP     | Patient 1                       | Patient 2             | Patient 3          | Patient 4          | Patient 5                     | Patient 6 |
|  | PaO <sub>2</sub> /FiO <sub>2</sub>   | before | 247                             | 368                   | 260                | >300               | >300                          | >300      |
|  |  | after  | 335                             | 326                   | 327                | >300               | >300                          | >300      |
|  | Lymphocytes, %   | before | 14.5                            | 2.8                   | N                  | N                  | 34.1                          | 25.2      |
|  |  | after  | 32                              | 12.5                  | N                  | N                  | 43.1                          | 41.5      |
|  | Monocytes, %   | before | 12                              | 1                     | N                  | 8.7                | N                             | 9.5       |
|  |  | after  | 12.4                            | 6.7                   | N                  | 6.8                | 7.7                           | 8.6       |
|  | CRP [mg/L]   | before | 319                             | 76                    | 19.5               | N                  | 6                             | 2.75      |
|  |  | after  | 46                              | 16                    | 9                  | N                  | 1.39                          | N         |
|  | IL-6 [pg/mL]   | before | 56.51                           | 14.44                 | 18.1               | 1.5                | 5.1                           | <1.5      |
|  |  | after  | 11.2                            | 9.36                  | 9.26               | N                  | 4.2                           | N         |
|  | Lung CT  | before | irregular multilobe infiltrates | extensive infiltrates | GGOs in right lung | GGOs in right lung | normal                        | normal    |
|  |  | after  | gradual absorption              | gradual absorption    | gradual absorption | gradual absorption | normal                        | normal    |
|  | Time from plasma transfusion to negative test in days  | -      | 5                               | 10                    | 2                  | 24                 | N/A (positive)                | 3         |
|  | Hospitalisation time in days   | -      | 59                              | 54                    | 49                 | 63                 | N/A (further hospitalisation) | 64        |
| Limitations                                    | <ul style="list-style-type: none"> <li>• Small sample size</li> <li>• Pre-print</li> <li>• Discrepancies in the results between the text description and table 2</li> </ul>  |        |                                 |                       |                    |                    |                               |           |
| Conclusions                                    | The condition of patients who received treatment with antiretroviral drugs and corticosteroids and who underwent plasma transfusion improved significantly.  |        |                                 |                       |                    |                    |                               |           |

GGOs – ground glass opacities; N/A – not applicable; N-normal & – no information on how the “general” condition was defined

**Table 9. Description of the methodology and results of Perotti 2020 – convalescent plasma**

| Perotti 2020   |   |                           |   |         |   |  |                    |
|--|---|---------------------------|---|---------|---|--|--------------------|
| Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma   |   |                           |   |         |   |  |                    |
| Methodology  | Population  |                           | Intervention  | Control | Standard clinical practice                    | Limitations  |                    |
| Single-arm, multi-centre study; Study type: proof of concept study; Patient recruitment: 25/03-21/04/2020<br>Observation time: 25/03-21/04/2020<br>Follow-up: until 28/04/2020<br>Country: Italy   | Average age (SD): 63 (12); Men: 61%<br>Average saturation (SD): 94% (3); average PaO2/FiO2 (SD): 128 (47)<br>Co-morbidities (2+): 41%<br>Severe ARDS: 33%, CPAP*: 70%; Intubation: 16%<br>Multilobe infiltrates in X-ray: 83%<br><u>Inclusion criteria:</u> ≥18 years of age, COVID-19 (laboratory-confirmed), moderate or severe ARDS (Berlin definition) for ≤10 days, increased CRP (approx. 3.6 x upper limit of normal or >1.8 mg/dl), patients requiring mechanical ventilation and/or CPAP<br><u>Exclusion criteria:</u> ARDS for >10 days, hypersensitivity or allergy to plasma components |                           | N=46<br>convalescent plasma (neutralising antibody titre: ≥1:160), unit volume: approx. 250-330 mL, infusion time: 30-60 min.,<br>24 patients – 1 unit,<br>21 patients – 2 units,<br>1 patient – 3 units<br>In addition, antibiotics, HCQ and anticoagulants were used: >80% of patients; | -       | in Poland – no established COVID-19 procedure | – Single-arm study<br>– No long-term observation,<br>– No results regarding the level of D-dimers and other inflammatory markers,<br>– Pre-print |                    |
| Results  |   |                           |   |         |   |  |                    |
| Endpoint   |   | Observation period (days) | Intervention  | Control | Relative parameter                            | Absolute parameter   | Clinical relevance |
| Mortality (%)  |   | 7                         | 6.5   | -       |   |  |                    |
| Increase in PaO2/FiO2 (units)  |   |                           | ↑ 112   | -       |   |  |                    |
| Patients with improved infiltrates on X-ray (%)  |   |                           | 23  | -       |   |  |                    |
| CRP levels   |   |                           | ↓ by 60%  | -       |   |  |                    |
| Ferritin levels  |   |                           | ↓ by 36%  | -       |   |  |                    |
| LDH levels   |   |                           | ↓ by 20%  | -       |   |  |                    |
| CPAP discontinuation   | n   |                           | 26  | -       |   |  |                    |
|  | median time in days   |                           | 2 (IQR 0-3)   |         |   |  |                    |
| Extubation   | n   |                           | 3   | -       |   |  |                    |
|  | median time in days   |                           | 2 (IQR 1-5)   |         |   |  |                    |
| Discharge from ICU, n  |   | 3                         | 2   | -       |   |  |                    |
| Use of ECMO, n   |   | 1 and 6                   | 2   | -       |   |  |                    |
| Severe AEs   | n patients  | 7                         | 4   | -       |   |  |                    |
|  | n events  |                           | 5   |         |   |  |                    |
| Conclusions: The obtained results indicate the possible benefits of plasma therapy; taking into account the lack of a control arm in the study, it is not possible to draw definitive conclusions. |   |                           |   |         |   |  |                    |

\* CPAP (Continuous Positive Airway Pressure);

\* Deaths on day 1, 4 and 6. Two deceased patients had comorbidities: diabetes, hypertension, and cancer. The third patient had a low PaO<sub>2</sub>/FiO<sub>2</sub> ratio (67) on the day of CP transfusion.

Baseline parameters of survivors: saturation, average: 94%, PaO<sub>2</sub>/FiO<sub>2</sub>, average: 131. Bilateral multilobe infiltrates in X-ray were observed in 89% of patients. All laboratory parameters increased.

### 2.1.1.3. Tocilizumab

| <b>Recommendation</b>   |
|---|
| In the absence of confirmed efficacy data, routine use of tocilizumab is not recommended and its use should be restricted to clinical trials. |

**Justification:**

This drug is a monoclonal antibody, an interleukin 6 receptor inhibitor (IL-6), high levels of which are found in the course of i.a. many inflammatory diseases<sup>155</sup>.

Currently, many publications report the so-called cytokine storm, involving IL-6, occurring in the course of COVID-19, especially in patients in severe and critical condition (Chen 2020, Huang 2020). In Zhou 2020, a retrospective study conducted in Wuhan, China between 29.12.2019 and 31.01.2020 on 191 hospitalised COVID-19 patients, in the group of patients whose infection ended in death (n=54), high and increasing IL 6 levels were observed since the beginning of laboratory blood tests until death (i.e. on days 4, 7, 10, 13, 16 and 19) . This was not observed in the convalescents (n=137). Differences in IL-6 levels between the deceased and survivors were statistically significant in every measurement time point, with the exception of the first one (i.e. day 4) (Zhou 2020).

The systematic review did not identify any completed, published randomised trials for tocilizumab in COVID-19, only case series descriptions.

The Luo 2020<sup>156</sup> clinical trial and the Xu 2020 retrospective study were also identified. In Luo 2020, the drug was given to 15 patients; of those 15, 2 were in moderate, 6 were in severe and 7 were in critical condition.

There was an improvement in the condition of one person, in 9, stabilisation of the disease was observed, the condition of 2 deteriorated and 3 died.

Xu 2020 describes a series of 21 cases of patients from China with COVID-19, in severe or critical condition, who were given tocilizumab as an additional therapy, in addition to routine treatment. Within a few days, the patients' temperature was back to normal and all other symptoms of the disease subsided. No serious adverse events were observed. Nineteen patients were discharged from the hospital after an average of 13.5 days (Xu 2020)<sup>157</sup>.

**Precautions:**

Particular caution should be applied when deciding to use tocilizumab treatment in patients with a history of recurrent infections or chronic infections or with concurrent diseases (e.g. diverticulitis, diabetes mellitus and interstitial lung disease) that may be predisposing to infections.

In patients treated with tocilizumab, severe hypersensitivity reactions, which are associated with infusions, and increased aminotransferase activity, including severe liver damage caused by the drug, such as acute liver failure, hepatitis and jaundice, were observed.

During biological treatment of patients with RA, cases of viral infection reactivation (e.g. hepatitis B) were reported.

Special caution should be applied when considering treatment initiation of tocilizumab in patients with a reduced number of platelets.

Doctors should be particularly sensitive to symptoms that may indicate newly developed central demyelinating disorders (SPC RoActemra<sup>158</sup>).

**Table 10. Description of the methodology and results of Luo 2020 and Xu 2020 – tocilizumab**

| Study  | Population  | Intervention   | Endpoints and results   | Limitations   | Conclusions   |
|--|---|--|---|---|---|
| <b>Luo 2020</b> <sup>159</sup> – retrospective study on a group of 15 patients treated between 27/01/2020 and 05/03/2020 in one Chinese hospital | <ul style="list-style-type: none"> <li>15 patients including 12 men and 3 women; median age 73 years (62-80), population divided into patients with mild symptoms (2 people), patients with moderate symptoms (6 people) and in critical condition (7 people). 10 people had at least one concurrent disease.</li> </ul>  | <ul style="list-style-type: none"> <li>One dose of tocilizumab ranging from 80 to 600 mg</li> <li>8 patients were treated with tocilizumab in combination with methylprednisolone</li> <li>5 people received 2 or more doses of tocilizumab</li> </ul> | <ul style="list-style-type: none"> <li>CRP and IL-6 levels</li> </ul> <p><b>RESULTS:</b></p> <ul style="list-style-type: none"> <li>In the case of 4 critically ill patients who received one dose of tocilizumab, 3 died and the CRP level in the remaining patient was not back to normal range during one week of observation. In the remaining 11 patients, the CRP levels were in the normal range or close to normal during the observation period.</li> <li>IL-6 levels before administration of tocilizumab ranged from 16.4 to 627.1 pg/mL. After treatment initiation, the IL-6 level in the serum of 10 patients (66.7%) showed a tendency to increase and then decrease rapidly. One patient showed a sustained decrease in IL-6 after treatment with tocilizumab in combination with methylprednisolone</li> </ul>   | <ul style="list-style-type: none"> <li>In addition to TOC, 8 patients were also treated with methylprednisolone</li> <li>5 patients received more than one dose of tocilizumab</li> </ul> | <ul style="list-style-type: none"> <li>The IL-6 level tends to increase further and then decrease in the majority of patients after initiation of tocilizumab treatment.</li> <li>Tocilizumab seems to be an effective treatment option in COVID-19 patients at risk of cytokine storm.</li> <li>Critically ill patients with increased IL-6 levels should be treated with a repeated dose of tocilizumab.</li> </ul> |
| <b>Xu 2020</b> <sup>160</sup> retrospective study on a group of 21 patients treated between 05/02/2020 and 14/02/2020 in two Chinese hospitals   | <ul style="list-style-type: none"> <li>21 patients including 18 men and 3 women</li> <li>Average age <math>56.8 \pm 16.5</math> years, from 25 to 88 y.o. The condition of 17 patients (81.0%) was assessed as severe and 4 (19.0%) as critical.</li> <li>The condition was assessed as severe when any of the following conditions were met: (1) respiration rate <math>\geq 30</math> breaths / min; (2) SpO<sub>2</sub> <math>\leq 93\%</math> while breathing in room air; (3) PaO<sub>2</sub> / FiO<sub>2</sub> <math>\leq 300</math> mmHg.</li> <li>The condition was considered critical when one of the following conditions was met: (1) respiratory failure requiring mechanical ventilation; (2) shock; (3) in combination with other organ failure, qualifying for admission to the ICU.</li> </ul> | <ul style="list-style-type: none"> <li>One dose of tocilizumab</li> <li>3 patients received tocilizumab twice</li> </ul>   | <p><b>RESULTS</b></p> <ul style="list-style-type: none"> <li>On the first day after treatment with tocilizumab, the body temperature drops to normal values</li> <li>Reduction of clinical symptoms in subsequent days</li> <li>One patient did not require further oxygen therapy.</li> <li>On the fifth day after treatment, an abnormal white blood cell number was found in only two patients (2/19, 10.5%) (mean: <math>5.25 \pm 2.11 \times 10^9 / L</math>). The percentage of lymphocytes in 10 patients (10/19, 52.6%) was back to normal (mean: <math>22.62 \pm 13.48\%</math>).</li> <li>CRP was back to normal in 84.2% of patients (16/19, mean: <math>2.72 \pm 3.60</math> mg / L) in day five of treatment</li> <li>Nineteen patients (90.5%) were discharged from the hospital, including two who were assessed as critical at the time of inclusion in the study</li> <li>The mean time of hospitalisation after tocilizumab treatment amounted to <math>13.5 \pm 3.1</math>.</li> </ul> | <ul style="list-style-type: none"> <li>3 patients received more than one dose of tocilizumab</li> <li>No control group</li> </ul>   | <ul style="list-style-type: none"> <li>Tocilizumab effectively alleviates clinical symptoms and inhibits deterioration of patients with COVID-19.</li> </ul>  |

#### 2.1.1.4. Chloroquine / hydroxychloroquine

| <b>Recommendation</b>   |
|---|
| In the absence of confirmed efficacy data, routine use of hydroxychloroquine/chloroquine is not recommended; their use should be restricted to clinical trials. |

##### **Justification:**

One RCT comparing efficacy and safety of chloroquine (CQ) with lopinavir/ritonavir (L/R) in COVID-19 and one RCT study comparing two chloroquine dosing regimens in COVID-19 – Borba 2020 were identified (**Błąd! Nie można odnaleźć źródła odwołania.**).

Two RCTs have been identified, one of them blind – Chen\_Z 2020<sup>161</sup> and one of them open – Chen\_J 2020<sup>162</sup>), concerning efficacy and safety of hydroxychloroquine in COVID-19 therapy. In addition, a retrospective, comparative observational study with a matched control group Mahévas 2020<sup>163</sup> that compares hydroxychloroquine to standard therapy was found, as well as Gautret 2020a<sup>164</sup>, a non-randomised study in which some patients taking hydroxychloroquine received azithromycin as a prophylaxis of bacterial infections and an observational study of the clinical efficacy of hydroxychloroquine in combination with azithromycin (Gautret 2020b<sup>165</sup>) and, Molina 2020<sup>166</sup>, a series of 11 cases in which hydroxychloroquine therapy in combination with azithromycin was applied in line with the Gautret 2020a dosage scheme, were found. The results of these studies were presented along with a discussion on azithromycin.

##### **Precautions:**

Special care should be taken in patients with initial prolonged QT-interval and/or taking other drugs that prolong QT-interval. It is recommended to perform an initial ECG or telemetry monitoring to assess QT in patients > 50 years old, with a previous or recent history of heart disease or other factors that may prolong QT. If, in the opinion of the practitioner, the benefits of hydroxychloroquine outweigh the risk in patients with prolonged QT-interval or using other drugs that prolong QT-interval, QT-interval should be reassessed by ECG or telemetry around day 3 of hydroxychloroquine treatment. Should there be any doubt, a clinical pharmacologist is to be consulted. Low-risk patients do not require an initial ECG or continuous monitoring unless the medical team decides otherwise. Other risks associated with the use of these drugs include arrhythmias, myocardial damage, bone marrow suppression and hypoglycaemia, therefore patients should be monitored for these adverse effects. Chloroquine can rarely cause neurological disorders (it lowers the seizure threshold) and psychosis, which should be given special attention in isolated patients.<sup>167,168</sup>

**Table 11. Description of the methodology and results of Huang 2020 – chloroquine**

| Huang 2020   |   |  |   |   |  |                    |
|--|---|--|---|---|--|--------------------|
| Treating COVID-19 with Chloroquine   |   |  |   |   |  |                    |
| Methodology  | Population  | Intervention                                   | Control   | Standard clinical practice  | Limitations  |                    |
| RCT, single-centre<br>Study conducted from 27/01 to 15/02/2020   | N=22<br>Age: 44.0 (36.5-57.5);<br>Severe cases, CQ: 30% vs LPV/r: 41.67%;<br><br>Patients with rRT-PCR-confirmed SARS-CoV-2 infection aged ≥ 18 years old | Ni=10<br>CQ<br>1-10 days: 500 mg p.o.<br>2 x 1 | Nk=12<br>Lopinavir/Ritonavir (LPV/r)<br>1-10 days: 400/100 mg p.o.<br>2 x 1 | Standard clinical practice: in Poland – no established COVID-19 procedure | <ul style="list-style-type: none"><li>• small sample size;</li><li>• age difference between the arms;</li><li>• different time period from onset;</li><li>• no randomisation description;</li><li>• results from an uncorrected manuscript</li></ul> |                    |
|  | Women: 40.9%  | 70%  | 50%   |   |  |                    |
|  | Severe cases  | 30%  | 41.67%  |   |  |                    |
| Results  |   |  |   |   |  |                    |
| Endpoint   | Observation period (days)   | Intervention                                   | Control   | RR (95% CI)   | NNT/ NNTH (95% CI)   | Clinical relevance |
| Negative rRT-PCR result on COVID-19 RNA  | 7   | 70   | 58.33   | 1.2 (0.60; 2.40)  | -  | Surrogate          |
|  | 10  | 90   | 75  | 1.2 (0.84; 2.00)  | -  |                    |
|  | 14  | 100  | 91.67   | 1,09 (1; 1.33)  | -  |                    |
| Improvement in CT imaging results  | 10  | 20   | 8.33  | 2,4 (0.14; 12.32)   | -  | Surrogate          |
|  | 14  | 100  | 75  | 1,33 (1.00; 2.00)   | -  |                    |
| Discharged from hospital   | 14  | 100  | 50  | 2 (1.33; 4.00)  | 2 (1.3; 4.6)*  | Surrogate          |
| Clinical improvement in 10 days  | -   | 80   | 58.33   | 1.37 (0.80; 2.80)   | -  | Surrogate          |
| Total adverse events during treatment period   | 10  | 90   | 83.33   | 1.08 (0.78; 1.5)*   | -  |                    |
| The analysis indicates no statistically significant differences in the following adverse events: vomiting, abdominal pain, nausea, diarrhoea, dizziness, headache, psychosis, rash or itching, coughing, dyspnoea (shortness of breath)  |   |  |   |   |  |                    |
| Conclusions: The study compared the results of two therapies, both of which had no previous evidence of efficacy in COVID-19 infection, so appropriate control, which in this case would be symptomatic treatment, was not applied. The study did not reveal a predominance of chloroquine over lopinavir/ritonavir or vice versa. However, it is not known whether any of these therapies are effective or which therapy was the control for the other therapy. The assessment was performed using surrogate endpoints, which do not have a significant clinical relevance in a disease with a significant risk of mortality. Due to a very small number of patients and methodological issues, the result is very uncertain. |   |  |   |   |  |                    |

**Table 12. Description of the methodology and results of Borba 2020<sup>169</sup> – chloroquine**

| Borba 2020  |  |  |  |   |   |  |
|---|--|--|--|---|---|--|
| Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection  |  |  |  |   |   |  |
| Methodology   | Population   |  | Intervention   | Control   | Standard clinical practice  | Limitations  |
| <b>Double-blind RCT, phase IIb, single-centre;</b><br><b>Study time:</b><br><b>From 23/03/2020</b><br><br><b>Aim: to assess the safety and efficacy of CQ in the treatment of patients with severe respiratory syndrome due to SARS-CoV-2 infection</b> | N = 81 24.7% women; 10 women in the arm; Hospitalised adult patients with a respiratory rate > 24 rpm AND/OR with a heart rate > 125 bpm (no fever) AND/OR peripheral SpO2 <90% AND/OR shock is included (defined as an average arterial pressure lower than 65 mmHg, with the need for vasopressors or oliguria or low-conscious patients).<br><br>Co-morbidities: hypertension (45.5%), alcohol abuse (27%), diabetes (25.5%)<br><br>Some patients (19) were included on the basis of SARS-CoV-2 suspected clinically and epidemiologically<br><br>Patients with ARDS received intravenous ceftriaxone/azithromycin starting from day 0. Oseltamivir was used in patients with suspected influenza infection |  | Nhd=41<br><br>High dose (CQhd) –<br><br>Days 0-10: 2x4 (150mg) =600mg CQ<br>total CQ dose=12g;<br><br>Not all patients have completed the study by day 13. | Nld=40<br><br>Low dose (CQld)–<br><br>Day 0: 1x3(150mg)=450 mg CQ+PLC<br>Days 1-4: 450 mg CQ + PLC<br>Days 5-9: PLC<br>total CQ dose=2.7g<br><br>Not all patients have completed the study by day 13. | in Poland – no established COVID-19 procedure                       | <ul style="list-style-type: none"><li>• small sample size; in line with the study design, the sample should include 440 patients;</li><li>• age difference between patients within the arms – the arm with the higher CQ dose included older patients;</li><li>• different time period from onset to treatment</li><li>• the higher CQ dose arm included more patients with a history of heart disease;</li><li>• the results are preliminary, they do not refer to the primary endpoint (mortality) on day 28 of the study;</li><li>• the control arm received CQ in addition to PLC</li></ul> no exclusion criteria based on the QTc segment duration; |
| Results   |  |  |  |   |   |  |
| Endpoint  | Therapy duration (days)  | Intervention   | Control  | RR (95% CI)   | NNT/MD (95% CI)   | Clinical relevance   |
| Death within 13 days  | 13   | 16/41 (39%) <sup>#</sup><br>14/31 (45.2%) <sup>***</sup> | 6/40 (15%) <sup>#</sup><br>5/31 (16.13%) <sup>***</sup>  | <b>2.6 (1.13; 5.97)<sup>**</sup></b><br><b>2.8 (1.15; 6.83)<sup>***</sup></b>   | <b>5 (2.3; 18.4)<sup>**</sup></b><br><b>4 (2; 14)<sup>***</sup></b> |  |
| Reduction of haemoglobin level <sup>Δ</sup> , %   |  | 7/24 (19.2%) <sup>#</sup><br>4/18 (22.2%) <sup>##</sup>  | 4/18 (22.2%) <sup>#</sup><br>3/11 (27.3%) <sup>##</sup>  | 1.31 (0.45; 3.81) <sup>#</sup><br>0.81 (0.22; 2.98) <sup>***</sup>  | -   |  |
| Increase in creatinine level <sup>ΔΔ</sup> , %  |  | 9/23 (39.1%) <sup>#</sup><br>8/18 (44.4%) <sup>##</sup>  | 7/15 (46.7%) <sup>#</sup><br>5/9 (55.6%) <sup>##</sup>   | 0.84 (0.40; 1.76) <sup>#</sup><br>0.8 (0.37; 1.74) <sup>***</sup>   | -   |  |
| Increase in phosphokinase level   |  | 7/14 (50.0%) <sup>#</sup>                                | 6/19 (31.6%) <sup>#</sup>  | 1.58 (0.68; 3.68) <sup>#</sup>  | <b>3 (2;11)</b>   |  |

| Borba 2020   |  |   |  |  |   |  |
|--|--|---|--|--|---|--|
|  |  | 6/9 (66.7%) <sup>##</sup>                               | 3/15 (20.0%) <sup>##</sup>                             | <b>3.33 (1.1; 10.14)<sup>***</sup></b>                             |   |  |
| Increase in CKMB level   |  | 7/13 (53.8%) <sup>#</sup><br>4/9 (44.4%) <sup>##</sup>  | 3/13 (23.1%) <sup>#,##</sup>                           | 2.33 (0.77; 7.10) <sup>#</sup><br>1.93 (0.56; 6.6) <sup>***</sup>  | - |  |
| QTcF>50ms <sup>^^</sup> , %  |  | 7/37 (18.9%) <sup>#</sup><br>7/29 (42.1%) <sup>##</sup> | 4/36 (11.1%) <sup>#</sup><br>1/27 (3.6%) <sup>##</sup> | 1.7 (0.54; 5.32) <sup>#</sup><br>6.52 (0.86; 49.56) <sup>***</sup> | - |  |
| Ventricular tachycardia, %   |  | 2/37 (2.7%) <sup>#</sup><br>2/31 (6.5%) <sup>#</sup>    | 0/36 (0%) <sup>#</sup><br>0/31 (0%) <sup>##</sup>      | 1.95 (0.18; 20.53) <sup>#</sup><br>5 (0.25; 100.08) <sup>***</sup> | - |  |
| <b>The authors' conclusions suggest that a higher dose of HQ should not be used in critical COVID-19 patients due to safety precautions, especially in combination with azithromycin and oseltamivir. They also indicate that these conclusions cannot be extrapolated to patients whose condition is not severe. It should also be borne in mind that the study is characterised by numerous limitations.</b> |  |   |  |  |   |  |

N/A – for statistically insignificant differences in RR, no absolute parameter values were estimated (NNT/NNH); SS – statistically significant differences; CKMB – creatine kinase isoenzyme MB; \* – Agency's own calculations; \*\* the estimations were taken directly from the study; ^ the results of reduced haemoglobin level by more than 3 g/dL or by 30% from the initial value are presented; ^^ increase by 30% or more; ^^ Serious adverse effects associated with the treatment were QT prolongation corrected for heart rate according to Fredric's formula (QTcF); #general population; ##population with confirmed COVID-19; \$ the deceased patients included 5 patients from the CQld arm (out of 6 deaths – 83.3%) with confirmed COVID-19 and 14 patients from the CQhd arm (out of 16 deaths – 87.5%).

**Table 13. Description of the methodology and results of Chen Z. 2020<sup>161</sup> – hydroxychloroquine**

| Chen Z 2020  |  |   |  |   |   |                    |
|--|--|---|--|---|---|--------------------|
| Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial   |  |   |  |   |   |                    |
| Methodology  | Population   | Intervention  | Control  | Standard clinical practice                    | Limitations   |                    |
| RCT, double-blind, single-centre; Study conducted from 04/02/2020 to 28/02/2020  | N = 62 patients<br>Average age: 44.7 (15.3)<br>men: 46.8% (n=29)<br>Hospitalised adults (≥18 years old) with positive rRT-PCR, with pneumonia confirmed by chest CT, with SaO2/SPO2 >93% or consenting to random treatment allocation and refraining from participation in other studies | n=31<br><br>HCQ 200 mg 2 x 1 (5 days) +<br>Standard therapy | n=31<br>PLC +<br>Standard therapy (oxygen therapy, antivirals, antibacterials, immunoglobulins, with or without corticosteroids) | in Poland – no established COVID-19 procedure | – small sample size;<br>– inconsistent inclusion/exclusion criteria between the report and the study protocol in terms of the arms to be compared and the number of exclusive groups, analysed endpoints, age of patients eligible for the study<br>– risk of patient selection error;<br>– use of antiviral and antibacterial therapies as part of standard therapy (no information on the percentage of patients taking any antiviral drugs); |                    |
| Results  |  |   |  |   |   |                    |
| Endpoint   | Therapy duration (days)  | Intervention  | Control  | RR (95% CI)                                   | NNT/MD (95% CI)   | Clinical relevance |
| Average time to normalise body temperature (SD)*   | 5  | 2.2 (0.4) days  | 3.2 (1.3) days   |   | MD=-1 (-1.48; -0.52)  | surrogate          |
| Average time until coughing subsides (SD)  |  | 2.0 (0.2) days  | 3.1 (1.5) days   |   | MD=-1.1 (-1.63; -0.57)  | surrogate          |
| Progression to severe disease  |  | 0/31 (0%)   | 4/31 (12.9%)   | 0.11 (0.01; 1.98)                             | -   |                    |
| Improvement in pneumonia shown in the CT   | 6  | 25/31 (80.6%)   | 17/31 (54.8%)  | 1.47 (1.02; 2.11)                             | NNT=4 (2.1; 29.1)   | surrogate          |
| Moderate improvement in pneumonia in the CT  |  | 6/31 (19.4%)  | 12/31 (38.7 %)   | 0.5 (CI: 0.21; 1.16)                          | -   | surrogate          |
| Significant improvement in pneumonia demonstrated in the CT  |  | 19/31 (61.3%)   | 5/31 (16.1%)   | 3.8 (1.62; 8.89)                              | NNT=3 (1.5; 4.2)  | surrogate          |
| Adverse events: total  | 5  | 2/31 (6.4 %)  | 0/31 (0%)  | 5 (0.25; 100.08)                              | -   |                    |
| Conclusions: Clinical trial of HCQ assessment against placebo demonstrated shortening of time to temperature normalisation and coughing cessation as well as greater improvement of radiological image in the group treated with HCQ. A study with a small population size, a short observation period and no clinically relevant endpoints. |  |   |  |   |   |                    |

N/A – for statistically insignificant differences in RR, no absolute parameter values were estimated (NNT/NNH); SS – statistically significant differences; CKMB – creatine kinase isoenzyme MB; \* – Agency's own calculations; \*\* the estimations were taken directly from the study; ^ the results of reduced haemoglobin level by more than 3 g/dL or by 30% from the initial value are presented; ^ increase by 30% or more; ^^ Serious adverse effects associated with the treatment were QT prolongation corrected for heart rate according to Fredric's formula (QTcF); #general population; ##population with confirmed COVID-19; \$ the deceased patients included 5 patients from the CQld arm (out of 6 deaths – 83.3%) with confirmed COVID-19 and 14 patients from the CQhd arm (out of 16 deaths – 87.5%).

**Table 14. Description of the methodology and results of Chen J. 2020<sup>162</sup> – hydroxychloroquine**

| Chen J 2020   |  |                                       |  |   |   |  |                       |
|---|--|---------------------------------------|--|---|---|--|-----------------------|
| A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19   |  |                                       |  |   |   |  |                       |
| Methodology   | Population   |                                       | Intervention   | Control   | Standard clinical practice                    | Limitations  |                       |
| RCT, non-blinded, single-centre;<br>Analysis of data on 0, 3, 5, 7 days after inclusion in the study<br>Study conducted from 06/02/2020 to 25/02/2020   | N = 30<br><br>Hospitalised adults (≥18 years old) with diagnosed pneumonia caused by 2019-nCoV |                                       | n=15<br><br>HCQ 400 mg 1x1 (5 days)<br><br>+<br>Standard therapy | n=15<br><br>standard therapy (symptomatic treatment, nebulisation, oxygen therapy, antiviral drugs: IFN- α, lopinavir / ritonavir, possibly antibacterial drugs | in Poland – no established COVID-19 procedure | - small sample size<br><br>- use of antiviral drugs in standard therapy (all patients received IFN-α in nebulisation, 12 (80.0%) in the study arm and 10 (66.7%) in the control arm received Arbidol (umifenovir); 2 (13.3%) were treated with lopinavir/ritonavir<br><br>- publication in Chinese |                       |
|   | Average age  |                                       | 50.5±3.8 years   | 46.7±3.6 years  |   |  |                       |
|   | Men  |                                       | 60%  | 80%   |   |  |                       |
| Results   |  |                                       |  |   |   |  |                       |
| Endpoint  |  | Thera<br>py<br>durati<br>on<br>(days) | Intervention   | Control   | RR (95% CI)                                   | NNT/MD (95% CI)  | Clinical<br>relevance |
| Virus absent in throat swab, sputum, lower respiratory tract discharge (%)  |  | 7                                     | 86.4   | 93.3  | 0.93 (0.73; 1.18)                             | -  | surrogate             |
| Median time to negative virus result days (days)  |  | 14                                    | 4 (1-9)  | 2 (1-4)   |   | -  |                       |
| Median time to normalise the temperature days (days)  |  |                                       | 1 (0-2)  | 1 (0-3)   |   | -  | surrogate             |
| Radiological progression in CT (%)  |  |                                       | 33.3   | 46.7  | 0,71 (0.29; 1.75)                             | -  | surrogate             |
| Percentage of patients with critical course of disease (%)  |  |                                       | 6.66   | 0   | 3 (0.13; 68.26)                               | -  |                       |
| Adverse effects according to CTCAE v5.0   |  |                                       | 26.7   | 20  | 1,33 (0.36; 4.97)                             | -  |                       |
| Conclusions: The study did not demonstrate statistically significant differences; therefore, it is impossible to draw clear conclusions on its basis. No results for mortality have been presented. |  |                                       |  |   |   |  |                       |

**Table 15. Description of the methodology and results of Tang 2020<sup>170</sup> – hydroxychloroquine**

| Tang 2020 (ChiCTR2000029868)  |  |   |   |   |   |                    |
|---|--|---|---|---|---|--------------------|
| Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial   |  |   |   |   |   |                    |
| Methodology   | Population   | Intervention  | Control   | Standard clinical practice                    | Limitations   |                    |
| Randomised controlled trial (1: 1) non-blinded, stratified by disease severity (mild/moderate or severe) covering the period of 11-29/02/2020<br><br>Number of centres and place where the trial was conducted: 16 centres, China | N = 150<br>Average age = 46 years<br>Men = 55%<br>Average number of days from onset to randomisation = 16.6<br>Patients receiving additional drugs before randomisation = 88%<br>Patients with severe course of the disease = 1%<br>Study population (inclusion criteria): Adult patients (≥18 years) with RT-PCR-confirmed SARS-CoV-2 and a CT scan to determine the disease severity | N = 75 HCQ + standard therapy (SOC)<br><br>6 patients were withdrawn from the trial<br>HCQ.<br>Days 0-3: 1,200mg x 1<br>Until week 2: 800mg x 1 – mild/moderate condition<br>Until week 3: 800 mg x 1 – severe condition<br>The doses were modified in the event adverse reactions occurred | N = 75 standard therapy (SOC) in accordance with the national clinical guidelines for COVID-19 – control arm<br>Minimum requirements for the SOC: fluid supply, oxygen therapy, regular laboratory tests, SARS-CoV-2 tests, haemodynamic monitoring, intensive care | in Poland – no established COVID-19 procedure | - suboptimal randomisation;<br>- non-blinded<br>- small sample size (sample size was estimated at 360 patients – 180 patients per arm),<br>- the study was discontinued |                    |
|   | Diabetes:  | 16%   | 12%   |   |   |                    |
|   | Hypertension:  | 8%  | 4%  |   |   |                    |
| Results   |  |   |   |   |   |                    |
| Endpoint  | Therapy duration (days)  | Intervention  | Control   | RR/HR (95% CI)                                | NNT/NNH (95% CI)  | Clinical relevance |
| Negative SARS-CoV-2 (%)   | 28   | 85.4  | 81.3  |   | -   |                    |
| Median time to negative virus result (days)   |  | 8   | 7   | HR=0.85 (0.58; 1.23)                          | -   |                    |
| Alleviation of disease symptoms (%)   |  | 59.9  | 66.6  |   | -   |                    |
| Median time to normalise temperature (days)   |  | 19  | 21  | HR=1.01 (0.59; 1.74)                          | -   |                    |
| Median time to normalise CRP (days)   |  | 8   | 14  | HR=1.32 (0.64; 2.71)                          | -   |                    |
| Median time to normalise lymphocyte concentration (days)  |  | 15  | 15  | HR=1.16 (0.44; 3.04)                          | -   |                    |
| Total AEs (per protocol) (%)  |  | 30  | 8.8   | <b>RR=3.43 (1.55; 7.58)</b>                   | <b>NNH=5 (3.0; 11.3)</b>  |                    |
| Total AEs (ITT) (%)   |  | 28  | 9.3   | <b>RR=3 (1.36; 15.2)</b>                      | <b>NNH=6 (3.2; 15.2)</b>  |                    |
| Conclusions: The study did not demonstrate statistically significant differences; therefore, it is impossible to draw clear conclusions on its basis. No results for mortality have been presented.                               |  |   |   |   |   |                    |

**Table 16. Description of the methodology and results of Mahévas 2020<sup>163</sup> – hydroxychloroquine**

| Mahévas 2020  |   |   |  |   |   |                    |
|---|---|---|--|---|---|--------------------|
| Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data   |   |   |  |   |   |                    |
| Methodology   | Population  | Intervention  | Control  | Standard clinical practice                    | Limitations   |                    |
| Multi-centre retrospective comparative observational study with a matched control group; the data were collected from 4 French hospitals;<br><br>12/03/2020-31/03/2020  | N=181<br>Hospitalised patients aged 18-80 with SARS-CoV-2 confirmed by PCR, requiring oxygen administration at ≥2L/min, but not intensive care.<br>No patient was treated with antiviral or anti-inflammatory drugs, including steroids or NSAIDs prior to transfer to the intensive care unit.<br>Patients receiving other experimental COVID-19 treatments (tocilizumab, lopinavir / ritonavir, remdesivir) within 48h from admission, with ARDS upon admission or requiring immediate transfer to the ICU were excluded. | n=84<br>HCQ 600 mg 1 x 1 + standard therapy +<br>18 received AZM<br>52% received amoxicillin with clavulanic acid | n=97<br>Standard therapy<br>HCQ was not used, but 8/97 received HCQ at a later time<br><br>29% received AZM<br>28% received amoxicillin with clavulanic acid | in Poland – no established COVID-19 procedure | <ul style="list-style-type: none"><li>- no information on the length of HCQ treatment</li><li>- study quality – observational study with a matched control group,</li><li>- higher percentage of men in the HCQ group and higher percentage of patients with lung involvement at &gt;50%, based on a scan</li><li>- some patients in the control group received HCQ (8%), &gt;48h from hospitalisation;</li><li>- different percentages of the population using AZM and amoxicillin</li></ul> |                    |
|   | Median age: 60 years (IQR: 52-68)   | 59 (IQR: 48–67)   | 62 (IQR: 53–68)  |   |   |                    |
|   | Men: 71.1%  | 78.3%   | 64.9%  |   |   |                    |
|   | Patients with lung involvement at >50%, CT scan: 16.9%  | 21.9%   | 12.1%  |   |   |                    |
|   | Median time from onset of symptoms to admission: 7 days (IQR: 5-10 days)  | 8 days (IQR: 6–10)  | 7 days (IQR: 4-10);  |   |   |                    |
| Results   |   |   |  |   |   |                    |
| Endpoint  | Therapy duration (days)   | Intervention  | Control  | HR (95% CI)                                   | NNT/MD (95% CI)   | Clinical relevance |
| Overall survival (%)  | 21 days   | 89  | 91   | 1.2 (0.4; 3.3)                                | -   |                    |
| Survival without ICU transfer (%)   |   | 76  | 75   | 0.9 (0.4; 2.1)                                | -   |                    |
| Survival without ARDS (%)   |   | 69  | 74   | 1.3 (0.7;2.6)                                 | -   |                    |
| Option to discontinue oxygen supply (%)   |   | 82  | 76   | 1.1 (0.9;1.3)                                 |   |                    |
| Discharge home or to a rehabilitation facility  |   | 80  | 80   | 1 (0.9; 1.2)                                  |   |                    |
| Changes in ECG requiring discontinuation of HCQ therapy (%)   |   | 10  | -  | -   | -   | -                  |
| Conclusions: The study did not demonstrate statistically significant differences; therefore, they do not indicate higher HCQ use compared to the control arm. A number of limitations, including lack of information on the drugs used in the control arm, should be borne in mind. |   |   |  |   |   |                    |

**Table 17. Description of the methodology and results of Gautret 2020a<sup>164</sup> – hydroxychloroquine**

| Gautret 2020a  |  |   |  |   |  |                    |
|--|--|---|--|---|--|--------------------|
| Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study   |  |   |  |   |  |                    |
| Methodology  | Population   | Intervention  | Control  | Standard clinical practice                  | Limitations  |                    |
| Retrospective cohort study<br><br>The study and control arm come from various centres<br><br>Study conducted from early March 2020 to 16 March 2020  | N=36<br>Average time from symptom onset: 4.0 days<br>Hospitalised patients with PCR-confirmed SARS-CoV-2 detected in in nasopharyngeal samples, >12 years old.<br><br>Patients with CQ or HCQ allergy and retinopathy, G6PD deficiency and QT prolongation were excluded | n=20<br>Hydroxychloroquine 200 mg 3x 1 for 10 days + symptomatic treatment and antibiotics (prophylaxis of bacterial superinfection.<br>AZM was used in 6 patients) | n=16<br>symptomatic treatment<br>no data on the treatment used | no established COVID-19 procedure in Poland | - loss of 6 patients from the study arm;<br>- the trial protocol did not include a control arm,<br>- the control arm comprised of patients from a different centre and those who did not agree to participate in the study;<br>- small sample size;<br>- age difference between the arms;<br>- no data on treatment in the control arm;<br>- the assessment time was modified in relation to the protocol and the results for days 7 and 14 after inclusion and after discharge were not presented,<br>- Journal Pre-Proof |                    |
|  | Average age: 45.1 (SD: 22.0)   | 51.2  | 37.3   |   |  |                    |
|  | Men  | 41.7%   | 37.5%  |   |  |                    |
|  | Asymptomatic   | 16.7%   | 25%  |   |  |                    |
|  | Median time from onset of symptoms to admission: 7 days (IQR: 5-10 days)   | 8 days (IQR: 6–10)  | 7 days (IQR: 4-10);  |   |  |                    |
| Results  |  |   |  |   |  |                    |
| Endpoint   | Therapy duration (days)  | Intervention  | Control  | RR (95% CI)                                 | NNT (95% CI)   | Clinical relevance |
| Negative PCR conducted on nasopharyngeal samples (PPA analysis)  | 3  | 50  | 6.3  | 8 (1.14; 56.1)                              | NNT = 3 (1.5; 5.3)   |                    |
|  | 4  | 60  | 25   | OR=4.5 (1.06; 19.04)                        | NNT = 3 (1.5; 20.8)  |                    |
|  | 5  | 65  | 18.8   | 3,47 (1.19; 10.1)                           | NNT = 3 (1.3; 5.6)   |                    |
|  | 6  | 70  | 12.5   | 5,6 (1.48; 21.13)                           | NNT = 2 (1.2; 3.2)   |                    |
| Negative PCR conducted on nasopharyngeal samples (post hoc analysis in subgroups)  | 3  | 35.7  | 6.3  | 5.71 (0.76; 43.23)                          | -  |                    |
|  | 4  | 50  | 25   | 2 (0.74; 5.42)                              | -  |                    |
|  | 5  | 50  | 18.8   | 2.67 (0.85; 8.39)                           | -  |                    |
|  | 6  | 57.7  | 12.5   | 4.57 (1.16; 18.05)                          | NNT = 3 (1.3; 7.1)   |                    |
| Conclusions: Very low reliability of the trial – small sample, very uncertain possibility of comparing the results of the experimental arm and the control arm which was made up partly of patients from other centres. Initially, both arms were characterised by significant differences, as clearly seen in terms of age – in this case, the fact that the average age of patients in the experimental arm was greater seems to favour positive results (Covid-19 has a worse prognosis in older patients). In addition, the result is distorted due to a large loss of patients from observation (6 out of 26) and the fact that azithromycin was used in only one arm (in 6 out of 20 patients) and, as suggested by subgroup analyses, this drug impacted the results. |  |   |  |   |  |                    |

**Table 18. Description of the methodology and results of Gautret 2020b<sup>165</sup> – hydroxychloroquine**

| Gautret 2020b  |   |  |         |   |  |                    |
|--|---|--|---------|---|--|--------------------|
| Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study                       |   |  |         |   |  |                    |
| Methodology  | Population  | Intervention   | Control | Standard clinical practice                    | Limitations  |                    |
| Single-centre observational study<br><br>duration of the study: from 03/03/2020 to 21/03/2020  | N=80<br>Median age: 52 years (18-88)<br>Men: 53.8%<br>Occurrence of ≥1 risk factor (hypertension, diabetes or chronic respiratory disease): 57.5%<br><br>Hospitalised patients with PCR-confirmed COVID-19.<br><br>The analysis included all patients treated with hydroxychloroquine and azithromycin for at least three days who were subject to observation for at least six days (the study included 6 patients using hydroxychloroquine with azithromycin from Gautret 2020a). | HCQ+AZM<br><br>HCQ: 200 mg 3x1<br>AZM:<br>Day 1: 500 mg<br>Days 2-5: 250 mg<br><br>Ceftriaxone was added in patients with pneumonia and NEWS^ at ≥5: 8%<br>79/80 patients were treated daily throughout the study period, which lasted up to 10 days | -       | in Poland – no established COVID-19 procedure | – single-arm study;<br>– no detailed information on the observation period;<br>– Journal Pre-Proof |                    |
| Results  |   |  |         |   |  |                    |
| Endpoint   | At least Observation period (days)  | Intervention   | Control | RR (95% CI)                                   | NNT (95% CI)   | Clinical relevance |
| Death (%)  | 6   | 1.2  |         |   |  |                    |
| Discharge (%)  |   | 81.2   |         |   |  |                    |
| Transfer to the ICU (%)  |   | 3.8  |         |   |  |                    |
| Implementation of oxygen therapy (%)   |   | 15   |         |   |  |                    |
| Average time from start of treatment to discharge (days)   |   | 4.1±2.2  |         |   |  |                    |
| Negative qPCR conducted on nasopharyngeal samples (%)  | 8   | 93   |         |   |  |                    |
| The study authors point out the need to continue research into HCV treatment for COVID-19. It should be noted that, due to the nature of the study, drawing clear conclusions on its basis is difficult. |   |  |         |   |  |                    |

<sup>^</sup> The national early warning score

**Table 19. Description of the methodology and results of Molina 2020<sup>166</sup> – hydroxychloroquine**

| Molina 2020   |  |                           |  |         |   |  |                    |
|---|--|---------------------------|--|---------|---|--|--------------------|
| No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection |  |                           |  |         |   |  |                    |
| Methodology   | Population / endpoint  |                           | Intervention   | Control | Standard clinical practice                    | Limitations                              |                    |
| Case series description (Infectious Diseases Department, AP-HP-Saint-Louis Hospital, France)  | N=11<br>Median age: 58.7 years (range: 20-77);<br>Percentage of men: 63.6%;<br>8/11 patients with significant co-morbidities associated with worse results (obesity: 2; solid tumours: 3; haematological cancers: 2; HIV infection: 1); 10/11 experienced fever at the start of treatment and received nasal oxygen therapy. |                           | <b>Hydroxychloroquine</b><br>600mg/day (200 mg, 3 per day) for 10 days<br><b>+Azithromycin</b><br>(500 mg on D1, then 250 mg per day for the next 4 days). | N/A     | in Poland – no established COVID-19 procedure | - no randomisation,<br>- no control arm. |                    |
|   | Hospitalised patients with PCR-documented SARS-CoV-2 detected in in nasopharyngeal samples.  |                           |  |         |   |  |                    |
| Results   |  |                           |  |         |   |  |                    |
| Endpoint  |  | Observation period (days) | Intervention   | Control | Relative parameter (95% CI)                   | NNT (95% CI)                             | Clinical relevance |
| Positive PCR test for SARS-CoV2 RNA   |  | 5-6                       | n=8/10** (80%, 95% CI: 49–94)<br><br>** not performed in deceased patients   | N/A     | N/A   | N/A                                      | -                  |
| Death   |  | 5                         | n=1/11 (9%)  | N/A     | N/A   | N/A                                      | -                  |
| Transfer to the ICU   |  | 5                         | n=2/11 (18%)   | N/A     | N/A   | N/A                                      | -                  |
| QT prolongation requiring discontinuation of therapy  |  | 5                         | n=1/11 (9%)  | N/A     | N/A   | N/A                                      | -                  |

**Table 20. Description of the methodology and results of Magagnoli 2020<sup>171</sup> – hydroxychloroquine**

| Magagnoli 2020   |  |   |   |  |   |  |                  |                |                    |
|--|--|---|---|--|---|--|------------------|----------------|--------------------|
| Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19  |  |   |   |  |   |  |                  |                |                    |
| Methodology  | Population   | Intervention                                |   | Control  | Standard clinical practice                    | Limitations  |                  |                |                    |
|  |  | 1   | 2   |  |   |  |                  |                |                    |
| Retrospective study;<br><br>Analysis of data from the VA Hospitals database<br><br>For 09/03/2020-11/04/2020   | N=368; Hospitalised patients with PCR-confirmed COVID-19.<br><br>Median age: 52 years (18-88)<br><br>Men: 53.8%<br><br>Occurrence of ≥1 risk factor (hypertension, diabetes or chronic respiratory disease): 57.5% | Ni1=97<br>HCQ.<br><br>+<br>standard of care | Ni2=113<br>HCQ+AZM<br><br>+<br>standard of care | Nk=158<br><br>+<br>standard of care<br><br><br>Use of AZM: 31.7% | in Poland – no established COVID-19 procedure | – retrospective documentation analysis<br>– no information about drug doses, time of pharmacotherapy or observation<br>– age of patients >65 years<br>– pre-print<br>– Initially, the patient groups differed in terms of some laboratory parameters, e.g. less than 800 lymphocytes were found in 24% of patients receiving HCQ, 31% receiving HCQ + AZA and only 13% without HCQ treatment |                  |                |                    |
|  | Median age (IQR) – years   | 70 (60-75)                                  | 68 (59-74)                                      | 69 (59-75)   |   |  |                  |                |                    |
|  | Median BMI (IQR) – kg/m²   | 30.5 (26-33.9)                              | 29.9 (25.7-36.6)                                | 29.6 (26.2-33.2)   |   |  |                  |                |                    |
| Results  |  |   |   |  |   |  |                  |                |                    |
| Endpoint   | Observation period (days)  | Intervention                                |   | Control  | RR/HR (95% CI)                                |  | NNT/NNH (95% CI) |                | Clinical relevance |
|  |  | 1   | 2   |  | Ni1vsNk                                       | Ni2vsNk  | Ni1vsNk          | Ni2vsNk        |                    |
| Death (%)  | -  | 27.8  | 22.1  | 11.4   | RR=2.44 (1.42; 4.19)<br>HR*=2.61 (1.10; 6.17) | RR=1.94 (1.11; 3.39)<br>HR*=1.14 (0.56; 2.32)  | NNH=7 (4; 17)    | NNH=10 (6; 62) |                    |
| Discharge (%)  |  | 72.2  | 77.9  | 88.6   | RR=0.81 (0.71; 0.93);                         | RR=0.88 (0.78; 0.98);  | NNT=7 (4; 17)    | NNT=10 (6; 62) |                    |
| Implementation of mechanical ventilation (%)   |  | 13.3  | 6.9   | 14.1   | RR=0.94 (0.5; 1.79);                          | RR=0.49 (0.22; 1.09);  |                  |                |                    |
| Deaths in patients not treated with mechanical ventilation   |  | 10  | 10.9  | 8.4  | RR=1.18 (0.54; 2.59);                         | RR=1.29 (0.61; 2.69);  |                  |                |                    |
| Mechanically-ventilated patients discharged from hospital  |  | 76.7  | 82.2  | 77.4   | RR=0.99 (0.86; 1.14);                         | RR=1.06 (0.94; 1.2);   |                  |                |                    |
| Deaths in patients treated with mechanical ventilation   |  |   |   |  | HR*=4.08 (0.77; 21.70)                        | HR*=1.20 (0.25; 5.77)  |                  |                |                    |
| Conclusions: A retrospective analysis of patients treated in veterans' hospitals in the US suggests a higher (more than double) mortality of patients who received hydroxychloroquine compared to those who did not receive this drug. The authors of the paper also carried out an analysis taking into account the differences in the initial severity of the patients' condition, which was less unfavourable for HQC, but did not completely eliminate the difference. The results of this study (characterised by very low reliability) do not prejudice the harmful effects of HQC in Covid-19. Concluding whether HQC is beneficial or harmful is only possible through experimental controlled trials with randomised selection for treatment groups. The analysed data suggest the need to apply great caution while attempting to use HQC and strongly confirm that HCQ cannot be used routinely in the treatment of Covid-19 patients, but only as part of well-controlled clinical trials. |  |   |   |  |   |  |                  |                |                    |

\* estimated by the authors of the publication using a proportional hazard model (Cox method)

**Table 21. Description of the methodology and results of Chorin 2020<sup>172</sup> – hydroxychloroquine**

| Chorin 2020  |   |                         |                         |  |                             |   |  |
|--|---|-------------------------|-------------------------|--|-----------------------------|---|--|
| QT Interval Prolongation and Torsade De Pointes in Patients with COVID-19 treated with Hydroxychloroquine/Azithromycin   |   |                         |                         |  |                             |   |  |
| Methodology  | Population  |                         |                         | Intervention   | Control                     | Standard clinical practice                    | Limitations  |
| Observational, retrospective, cohort study,<br><br>Data derived from 2 centres (NYU Langone, New York and San Paolo University Hospital). Data from patients observed up to 15/04/2020 were included   | N=251<br>64±13 years;<br>Men: 75%<br>Co-morbidities: Coronary artery disease: 12%; Hypertension: 54%<br>Chronic kidney disease: 11%; Diabetes: 27%; COPD: 7%; Heart failure: 3%<br>Receiving drugs for QTc prolongation:<br>1 drug: 27%, 2 drugs: 2%<br>Inclusion criteria: hospitalised adult patients with confirmed COVID-19 for whom ECG results (baseline and after therapy) are available<br>Average QTc value (ms): 439±29<br>Average JTc value (ms): 342±25 |                         |                         | HCQ+AZM<br><br>HCQ<br>Day 1: 400 mg 2x1<br>Days 2-5: 200 mg 2x1<br><br>AZM<br>Days 1-5: 500 mg 1x1 | -                           | in Poland – no established COVID-19 procedure | - patients treated with each drug as monotherapy were not included,<br>- short observation time after concluding the HCQ/AZM regimen<br>- retrospective nature of the study; |
|  | Subpopulations  | QRS<120ms               | QRS ≥120 ms             |  |                             |   |  |
|  | Average QTc value (ms)  | 434 ± 25                | 475 ± 33                |  |                             |   |  |
|  | Size  | 222                     | 29                      |  |                             |   |  |
| Results  |   |                         |                         |  |                             |   |  |
| Endpoint   |   | Therapy duration (days) | Intervention QRS<120 ms | Intervention QRS >120  | Relative parameter (95% CI) | NNT/MD (95% CI)                               | Clinical relevance   |
| Maximum QTc value (ms)   |   | 8                       | 473±36                  |  |                             |   |  |
| Maximum JTc value (ms)   |   |                         | 375±35                  |  |                             |   |  |
| Maximum QT (ms) in subpopulations  |   |                         | 469 ± 34                | -  |                             |   |  |
| JTc>410 ms %   |   |                         | -                       | 14   |                             |   |  |
| ΔQTc > 60 ms %   |   |                         | 20                      |  |                             |   |  |
| QT > 500 ms %  |   |                         | 13                      | -  |                             |   |  |
| Death due to respiratory or multiple organ failure %   |   |                         | 17.5                    |  |                             |   |  |
| TdP ( <i>torsades de pointes</i> ) %   |   |                         | 0.4 (1 patient)         |  |                             |   |  |
| The authors of the study suggest that an individual benefit/risk assessment be used prior to HCQ/AZM treatment. Daily ECG monitoring with therapy re-assessment is recommended if high risk markers appear (QTc> 500 ms or ΔQTc> 60 ms). Only partial resolution of QTc was observed 3 days after the end of therapy. This can be attributed to hydroxychloroquine's extended half-life, which is about 20 days. This discovery requires special attention when considering the discharge of patients receiving HCQ/AZM or planned outpatient treatment. |   |                         |                         |  |                             |   |  |

**Table 22. Description of the methodology and results of Mehra 2020 – chloroquine, hydroxychloroquine, macrolides**

| Mehra 2020  |  |               |                           |                 |                         |                       |   |  |                         |                         |                   |                   |                   |                   |                    |
|---|--|---------------|---------------------------|-----------------|-------------------------|-----------------------|---|--|-------------------------|-------------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis            |  |               |                           |                 |                         |                       |   |  |                         |                         |                   |                   |                   |                   |                    |
| Methodology   | Population   | Intervention  |                           |                 |                         | Contr ol              | Standard clinical practice                    | Limitations  |                         |                         |                   |                   |                   |                   |                    |
|   |  | A             | B                         | C               | D                       |                       |   |  |                         |                         |                   |                   |                   |                   |                    |
| Observational<br>20/12/2019-14/04/2020<br><br>Analysis of data from the register containing data from 671 hospitals from 6 continents | N=96,032<br>Women: 46.3%<br>Average age: 53.8±17.6<br>Average BMI: 27.6±5.5<br>Obesity: 30.7%<br>Hypertension: 26.9%<br>Hyperlipidaemia: 31.4%<br>Diabetes: 13.8%<br>COPD: 3.3%<br>Smokers: 9.9%<br>Former smokers: 17.2%<br>Immunosuppression: 3.0%<br>no SS differences in baseline characteristics of the patients between the arms | CQ<br>Na=1868 | CQ + MACR<br>*<br>Nb=3783 | HCQ.<br>Nc=3016 | HCQ + MACR*<br>Nd= 6221 | No HCQ/CQ<br>Nk=81144 | in Poland – no established COVID-19 procedure | - the possibility of immeasurable disturbing factors cannot be ruled out; therefore, no cause-and-effect relationship can be concluded between pharmacological treatment and survival;<br>- QT intervals were not measured,<br>- it has not been established whether the relationship between the increased risk of in-hospital death and the use of treatment regimens is directly related to their cardiovascular risk;<br>- no dose-related hazard analysis has been performed;<br>- antiviral therapy other than HCQ/CQ+/- macrolides were used in 40.5% |                         |                         |                   |                   |                   |                   |                    |
|   | Average daily dose (mg)  | 765±308       | 790±320                   | 596±126         | 597± 128                |                       |   |  |                         |                         |                   |                   |                   |                   |                    |
|   | Average time of receiving the drug   | 4.2±2.4       | 6.8±2.5                   | 4.2±1.9         | 4.3± 2.0                |                       |   |  |                         |                         |                   |                   |                   |                   |                    |
|   | qSOFA<1**  | 81.9          | 80.7                      | 82.1            | 80.3                    | 83                    |   |  |                         |                         |                   |                   |                   |                   |                    |
|   | SPO <sub>2</sub> <94%  | 11.2          | 10.9                      | 10.7            | 10.5                    | 9.5                   |   |  |                         |                         |                   |                   |                   |                   |                    |
| Results   |  |               |                           |                 |                         |                       |   |  |                         |                         |                   |                   |                   |                   |                    |
| Endpoint  | Average hospitalisation duration (days)  | Intervention  |                           |                 |                         | Contr ol              | HR (95% CI)                                   |  |                         |                         | NNH (95% CI)^     |                   |                   |                   | Clinical relevance |
|   |  | A             | B                         | C               | D                       |                       | AvsK  | BvsK   | CvsK                    | DvsK                    | Avs K             | Bvs K             | Cvs K             | Dvs K             |                    |
| Mortality (%)   | 9.1(±6.4)  | 16.4          | 22.2                      | 18.0            | 23.8                    | 9.3                   | 1.37<br>(1.22;<br>1.53)                       | 1.37<br>(1.27;<br>1.47)  | 1.34<br>(1.22;<br>1.46) | 1.45<br>(1.37;<br>1.53) | 14<br>(12;<br>19) | 8<br>(8;9)        | 12<br>(10;<br>14) | 7<br>(7;8)        |                    |
| Mechanical ventilation (%)  |  | 21.6          | 21.5                      | 20.4            | 20.0                    | 7.7                   |   |  |                         |                         |                   |                   |                   |                   |                    |
| De-novo ventricular arrhythmia (%)  |  | 4.3           | 6.5                       | 6.1             | 8.1                     | 0.3                   | 3.56<br>(2.76;<br>4.6)                        | 4.01<br>(3.34;<br>4.81)  | 2.37<br>(1.95;<br>2.9)  | 5.11<br>(4.36;<br>5.98) | 25<br>(21;<br>32) | 17<br>(15;<br>19) | 18<br>(15;<br>21) | 13<br>(12;<br>15) |                    |
| Transition to mechanical ventilation or death (%)   |  | 28.4          | 34.0                      | 29.1            | 34.1                    | 13.2                  |   |  |                         |                         |                   |                   |                   |                   |                    |
| Average number of days spent in ICU   |  | 4.3<br>(±6.8) | 4.9<br>(±8.1)             | 4.3<br>(±6.8)   | 4.7 (±7.8)              | 2.6<br>(±5.0)         |   |  |                         |                         |                   |                   |                   |                   |                    |
| Average number of days outside of ICU   |  | 8.8<br>(±6.2) | 9.0<br>(±6.6)             | 8.9<br>(±6.2)   | 9.1 (±6.7)              | 9.1<br>(±6.4)         |   |  |                         |                         |                   |                   |                   |                   |                    |

| Mehra 2020  |  |                |               |                |                 |                |  |  |
|---|--|----------------|---------------|----------------|-----------------|----------------|--|--|
| Average total number of hospitalisation days  |  | 13.2<br>(±9.1) | 13.8<br>(±11) | 13.2<br>(±9.3) | 13.8<br>(±10.7) | 11.7<br>(±8.4) |  |  |
| <p>Ventricular arrhythmias occurred statistically significantly more often in the treated arms than in the control population. The risk of death was also statistically significantly higher in the treatment arms compared to the control population. Age, BMI, black or Latin ethnicity (compared to white ethnicity), coronary artery disease, congestive heart failure, history of arrhythmia, diabetes, hypertension, hyperlipidaemia, COPD, active smoker status and immunosuppression were associated with a higher risk of in-hospital death. Female gender, Asian ethnicity, use of ACE inhibitors (but not angiotensin receptor blockers) and statins were associated with a reduced risk of in-hospital death. Despite statistically significant results, unfavourable for the use of HCQ/CQ+/-MACR, one should keep the retrospective nature of the study in mind and, therefore, possible interfering factors which significantly affect the result. Considering the above, it is doubtful whether drawing clear conclusions based on the above study is possible.</p> |  |                |               |                |                 |                |  |  |

\* Macrolides: only azithromycin or clarithromycin;

\*\* qSOFA (quick sequential organ failure assessment score) simplified scale of organ failure associated with sepsis;

\*\*\* oxygen saturation; ^ Agency's own calculations

**Table 23. Description of the methodology and results of Barbosa 2020 – hydroxychloroquine**

| Barbosa 2020  |  |                         |  |                          |   |   |                    |
|---|--|-------------------------|--|--------------------------|---|---|--------------------|
| Clinical Outcomes of Hydroxychloroquine in Hospitalized Patients with COVID-19: A Quasi-Randomized Comparative Study  |  |                         |  |                          |   |   |                    |
| Methodology   | Population   |                         | Intervention   | Control                  | Standard clinical practice                    | Limitations   |                    |
| Quasi-randomised comparative study, Swabs were collected: 19/03/2020-26/03/2020   | N=63<br>Women: 41.3%<br>Average age: 62.7±15.1<br><br>There were no statistically significant differences between the arms in terms of the number of high-risk co-morbidities, lymphocyte and neutrophil levels. |                         | Ni=32<br>HCQ+ supportive care<br><br>Day 0: 400 mg 2x1<br>Days 1-4: 200-400 mg 1x1 | Nk=31<br>Supportive care | in Poland – no established COVID-19 procedure | <ul style="list-style-type: none"><li>- quasi-randomisation – due to a difference in diagnosis (7-day difference) based on PCR</li><li>- no information about other drugs received by the patients</li><li>- small population size</li><li>- statistically significantly worse results of the assessment of the respiratory system in the HCQ arm than in the control arm</li></ul> |                    |
|   | Respiratory system assessment on a scale of 1-4*: 1.73±0.68  |                         | 1.94±0.67  | 1.52±0.63                |   |   |                    |
| Endpoint  |  | Therapy duration (days) | Intervention   | Control                  | RR (95% CI)                                   | NNT (95% CI)  | Clinical relevance |
| Mortality (%)   |  | 5                       | 12.9   | 3.13                     | 4.13 (0.49; 34.92)                            | -   |                    |
| Change in respiratory system assessment on a scale of 1-4*  |  |                         | +0.63±0.79   | +0,16±0,64               |   | -   |                    |
| Based on the scale used, the authors of the publication point out a deterioration in the respiratory system. Nonetheless, a number of study limitations should be taken into account, including a statistically significant difference to the disadvantage of the arm using HCQ in the initial respiratory system assessment, compared to the control arm. For the remaining endpoints, such as mortality, neutrophil to lymphocyte ratio, and change in lymphocyte levels, the differences were not statistically significant. The results regarding the subpopulation of patients over 50 years of age where the neutrophil to lymphocyte ratio exceeded 3.13, were analogous in terms of statistical significance to the results of the general population analysis. |  |                         |  |                          |   |   |                    |

\*Assessment on a 4-point scale: 1-room air, 2-oxygen supply without incubation, 3-oxygen supply with intubation, 4-death following intubation/ventilation;

**Table 24. Description of the methodology and results of Singh 2020 – hydroxychloroquine + azithromycin**

| Singh 2020   |  |                         |   |                               |   |   |                    |
|--|--|-------------------------|---|-------------------------------|---|---|--------------------|
| Outcomes of Hydroxychloroquine Treatment Among Hospitalized COVID-19 Patients in the United States- Real-World Evidence From a Federated Electronic Medical Record Network   |  |                         |   |                               |   |   |                    |
| Methodology  | Population   |                         | Intervention                              | Control                       | Standard clinical practice                    | Limitations   |                    |
| Analysis of retrospective observational data, Multi-centre<br><br>20/01/2020-01/05/2020<br><br>A global health research network – TriNetX (Cambridge, MA, USA) – was used  | N=1820<br><br>COVID-19 patients > 18 years of age<br><br>Selected out of 3,372 patients<br>The selection was aimed at closing the differences between arms, i.a. in terms of: age, sex or concomitant diseases |                         | Ni=910<br>HCQ.<br>+ AZM (in 799 patients) | Nk=910<br><br>Basic treatment | in Poland – no established COVID-19 procedure | - preprint<br>- no information about patients receiving other drugs in both the study and control arms, although patients who received other drugs as part of COVID-19 therapy were excluded from the study |                    |
|  | Hypertension   |                         | 62.75%                                    | 60.33%                        |   |   |                    |
|  | Average age (SD)   |                         | 62.17±16.81                               | 62.55±17.62                   |   |   |                    |
|  | Men  |                         | 53.95%                                    | 54.94%                        |   |   |                    |
| Endpoint   |  | Therapy duration (days) | Intervention                              | Control                       | RR (95% CI)                                   | NNT (95% CI)  | Clinical relevance |
| Mortality (%)  |  | 30                      | 11.43                                     | 11.98                         | 0.95 (0.74;1.23)                              |   |                    |
| Mechanical ventilation (%)   |  |                         | 5.05                                      | 6.26                          | 0.81 (0.55; 1.18)                             |   |                    |
| Conclusions: The results do not indicate statistically significant differences between the studied arms in terms of patient mortality or the need to implement mechanical ventilation. In addition, after isolating the group of patients receiving HCQ with AZM and comparing their results with results from the control arm, no statistically significant differences were found. |  |                         |   |                               |   |   |                    |

**Table 25. Description of the methodology and results of Singh 2020 – hydroxychloroquine**

| Singh 2020   |  |                         |   |                               |   |   |                    |
|--|--|-------------------------|---|-------------------------------|---|---|--------------------|
| Outcomes of Hydroxychloroquine Treatment Among Hospitalized COVID-19 Patients in the United States- Real-World Evidence From a Federated Electronic Medical Record Network   |  |                         |   |                               |   |   |                    |
| Methodology  | Population   |                         | Intervention                              | Control                       | Standard clinical practice                    | Limitations   |                    |
| Analysis of retrospective observational data, Multi-centre<br><br>20/01/2020-01/05/2020<br><br>A global health research network – TriNetX (Cambridge, MA, USA) – was used  | N=1820<br><br>COVID-19 patients above 18 years of age<br><br>Selected out of 3,372 patients<br>The selection was aimed at closing the differences between arms, i.a. in terms of: age, sex or concomitant diseases |                         | Ni=910<br>HCQ.<br>+ AZM (in 799 patients) | Nk=910<br><br>Basic treatment | in Poland – no established COVID-19 procedure | - preprint study<br>- no information about patients receiving other drugs in both the study and control arms, although patients who received other drugs as part of COVID-19 therapy were excluded from the study |                    |
|  | Hypertension   |                         | 62.75%                                    | 60.33%                        |   |   |                    |
|  | Average age (SD)   |                         | 62.17±16.81                               | 62.55±17.62                   |   |   |                    |
|  | Men  |                         | 53.95%                                    | 54.94%                        |   |   |                    |
| Endpoint   |  | Therapy duration (days) | Intervention                              | Control                       | RR (95% CI)                                   | NNT (95% CI)  | Clinical relevance |
| Mortality (%)  |  | 30                      | 11.43                                     | 11.98                         | 0.95 (0.74;1.23)                              |   |                    |
| Mechanical ventilation (%)   |  |                         | 5.05                                      | 6.26                          | 0.81 (0.55; 1.18)                             |   |                    |
| Conclusions: The results do not indicate statistically significant differences between the studied arms in terms of patient mortality or the need to implement mechanical ventilation. In addition, after isolating the group of patients receiving HCQ with AZM and comparing their results with results from the control arm, no statistically significant differences were found. |  |                         |   |                               |   |   |                    |

**Table 26. Description of the methodology and results of Kim 2020 – hydroxychloroquine, azithromycin**

| Kim 2020   |  |   |                |  |                           |   |                     |   |                    |
|--|--|---|----------------|--|---------------------------|---|---------------------|---|--------------------|
| Treatment Response to Hydroxychloroquine, Lopinavir/Ritonavir, and Antibiotics for Moderate COVID 19: A First Report on the Pharmacological Outcomes from South Korea  |  |   |                |  |                           |   |                     |   |                    |
| Methodology  | Population   | Intervention 1  |                | Intervention 2   | Control                   | Standard clinical practice                    |                     | Limitations   |                    |
| Retrospective cohort study<br><br>28/02-28/04/2020   | N=97<br><br>Patients with laboratory-confirmed COVID19 in moderate condition<br><br>Women: 64.4% | Ni1=22<br>HCQ 200 mg 2x1<br>+ AZM 500 mg 1x1 (3 days)<br>Cefixime 100 mg 2x1 used until remission of pneumonia<br>+ SoC |                | Ni2=35<br>Lopinavir 200 mg / ritonavir 50mg 2x1<br>+ AZM I Cefixime as in Ni1<br>+ SoC | Nk=40<br>Standard therapy | in Poland – no established COVID-19 procedure |                     | - the study included 358 patients, while data of 97 patients in moderate condition were subjected to analysis<br>- the patient characteristics in particular groups differed. With the exception of age, sex, changes in chest imaging, dyspnoea and laboratory blood results, the differences were not statistically significant<br>- the patients from the HCQ arm had worse results in terms of LDH, lymphocyte, CRP or WBC levels<br>- no data are available in the QT or retinopathy study |                    |
|  | Pathological changes in chest x-ray  | 95.5%   |                | 91.4%  | 17.9%                     |   |                     |   |                    |
|  | Average age of patients (years)  | 42.5  |                | 49   | 36.1                      |   |                     |   |                    |
|  | Dyspnoea   | 40.9%   |                | 31.4%  | 82.5%                     |   |                     |   |                    |
| Results  |  |   |                |  |                           |   |                     |   |                    |
| Endpoint   | Therapy duration (days)  | Intervention 1  | Intervention 2 | Control  | HR (95% CI)               |   | MD (95% CI)         |   | Clinical relevance |
|  |  |   |                |  | Ni1vsNi2                  | Ni1vsNk                                       | Ni1vsNi2            | Ni1vsNk   |                    |
| Number of days from start of therapy until a negative a result is obtained in PCR  |  | 15.3±3.8  | 19.1±5.7       | 20.7±10.3  | 0.49 (0.28; 0.87)         | 0.44 (0.25; 0.78)                             | -3.8 (-6.5; -1.1)   | -5.4 (-9.88; -0.92)   |                    |
| Number of days from start of therapy to discharge  |  | 16.5±4.0  | 19.9±5.8       | 20.7±7.8   | 0.53 (0.3; 0.93)          | 0.49 (0.28; 0.87)                             | -3.4 (-6.17; -0.63) | -4.2 (-7.7; -0.7)   |                    |
| Transfer to intensive care unit  |  | 4.5   | 11.4           | 0  |                           |   |                     |   |                    |
| Total adverse events (%)   |  | 31.8  | 34.3           | 2.5  |                           |   |                     |   |                    |
| No deaths or serious adverse events were reported. Tachycardia was reported in one patient in the HQ arm reported. No patient needed mechanical ventilation.   |  |   |                |  |                           |   |                     |   |                    |
| Authors' conclusions: The use of HQ in combination with antibiotics was associated with a shorter time from treatment initiation to the PCR result indicating the absence of virus, compared to the arm using LOP/R and standard treatment. No statistically significant differences were noted between the LOP/R and standard treatment arms. The addition of AZM and cefixime may have an additional benefit, however this requires further evaluation. It should be borne in mind that only patients in moderate condition (showing lower respiratory tract symptoms based on clinical or imaging assessment and saturation at >93%) were analysed. |  |   |                |  |                           |   |                     |   |                    |

**Table 27. Description of the methodology and results of Yu 2020 – hydroxychloroquine**

| Yu 2020  |   |                         |  |  |   |  |                    |
|--|---|-------------------------|--|--|---|--|--------------------|
| Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19   |   |                         |  |  |   |  |                    |
| Methodology  | Population  |                         | Intervention   | Control                                  | Standard clinical practice                    | Limitations  |                    |
| Retrospective study,<br><br>01/02/2020 - 04/04/2020  | N=550 (344 men) median age=68<br><br>Patients had to meet one of the following criteria: requiring respiratory failure and mechanical ventilation; septic shock during hospitalisation; failure of other organs which required ICU monitoring and treatment |                         | Ni=48<br>HCQ p.o. 200 mg 2x1 (7-10 days) + basic treatment (lopinavir and ritonavir, entecavir hydrate or ribavirin, intravenous immunoglobulin immunoenhancer, antibiotics, interferon) | Nk=502<br><br>Basic treatment (as in Ni) | in Poland – no established COVID-19 procedure | - significantly fewer patients in the intervention arm |                    |
|  | Baseline IL-6 (pg mL <sup>-1</sup> )  |                         | 22.2 (8.3-118.9)   | (21.3 (8.8-62.8)                         |   |  |                    |
| Endpoint   |   | Therapy duration (days) | Intervention   | Control                                  | Relative parameter HR (95% CI)                | NNT (95% CI)   | Clinical relevance |
| Mortality (%)  |   | 7-10                    | 18.8   | 47.4                                     | 0.31 (0.16; 0.61)*<br>0.36 (0.18; 0.75)**     | 4 (6, 3)*  |                    |
| Baseline IL-6 cytokine (pg mL <sup>-1</sup> )  |   |                         | 5.2 (3.0-23.4)   | 20.2 (6.1-94.4)                          |   |  |                    |
| Length of hospital stay prior to death (days)  |   |                         | 15 (10-21)   | 8 (4-14)                                 |   |  |                    |
| Conclusions: The results of the study indicate statistically significantly lower mortality in the intervention arm compared to the control arm. In addition, there was a significantly higher decrease in IL-6 cytokine levels in the HCQ arm compared to the arm using basic treatment. The study reported a lower death rate in the arm where HCQ treatment was initiated at an early stage (within 5 days of admission) than in the arm in which treatment was initiated later: 9.1% (n=11) vs 21.6% (n=37), however, the difference was not statistically significant. |   |                         |  |  |   |  |                    |

\*unadjusted results \*\*adjusted results;

**Table 28. Description of the methodology and results of Ramireddy 2020 – hydroxychloroquine, azithromycin**

| Ramireddy 2020   |   |                         |              |                  |           |   |   |              |                    |
|--|---|-------------------------|--------------|------------------|-----------|---|---|--------------|--------------------|
| Experience with Hydroxychloroquine and Azithromycin in the COVID-19 Pandemic: 1 Implications for QT Interval Monitoring  |   |                         |              |                  |           |   |   |              |                    |
| Methodology  | Population  | Intervention            |              |                  | Control   | Standard clinical practice                    | Limitations   |              |                    |
|  |   | A                       | B            | C                |           |   |   |              |                    |
| Retrospective study<br><br>21/01/2020-04/04/2020<br><br>Tisdale score and Elixhauser score were used   | N=98<br>Men: 61%<br>Average age: 62±17<br><br>Patients with confirmed (n=73) or suspected COVID-19 (n=25), who underwent at least 2 ECG tests between 1/01/20-4/05/20, no later than 2 days from the start of the study<br><br>Patients with ventricular arrhythmias, atrial fibrillation or flutter, supraventricular tachycardia or ECG results which prevented accurate QTc indication were excluded<br>Average QTc = 448±29 ms<br>20% of patients had QTc>470ms | AZM<br>Na=27            | HCQ<br>Nb=10 | HCQ+AZM<br>Nc=61 |           | in Poland – no established COVID-19 procedure | - pre-print<br>- small population<br>- no control group, comparison was made only between AZM and HCQ+AZM<br>- no results for the subpopulation using only HCQ<br>- no information on the use of drugs other than HCQ and AZM |              |                    |
|  | Average QTc value (ms)  | 463±39                  |              | 439±20           |           |   |   |              |                    |
| Endpoint   |   | Therapy duration (days) | Intervention |                  |           | Control                                       | RR (95% CI)   | NNT (95% CI) | Clinical relevance |
| Average QTc value (ms)   |   |                         | 464±38       |                  | 457±38    |   |   | -            |                    |
| Average change in QTc vs baseline (ms)   |   |                         | 0.5±40.3     |                  | 17,2±39,0 |   |   | -            |                    |
| Critical QTs** (%)   |   |                         | 11           |                  | 8         |   |   |              |                    |
| Change in QTs ≥60ms (%)  |   |                         | 15           |                  | 12        |   |   |              |                    |
| No statistically significant differences between the average change in QTc were observed in comparison with the arm using AZM and HCQ + AZM. At the same time the small population size, which may contribute to the inability to achieve statistical significance, should be taken into account. It is worth noting that although the difference in the average change is much higher in the population using HCQ + AZM, the mean baseline value for this arm is lower than in the arm using AZM as monotherapy. Torsades de pointes was not reported in any patient. It is worth noting that statistically significant mean QTc prolongation was observed only in men (average increase: 18±43 ms), while in women, a slight decrease was noted. |   |                         |              |                  |           |   |   |              |                    |

\* Tisdale score is used to assess the risk of QT prolongation above 500 ms in hospitalised patients;

\*\* ≥500ms (QRS <120ms) or ≥550ms (QRS ≥120ms)

**Table 29. Description of the methodology and results of Ip 2020 – hydroxychloroquine**

| Andrew 2020   |  |  |                      |                |                |  |   |   |      |      |               |                    |
|---|--|--|----------------------|----------------|----------------|--|---|---|------|------|---------------|--------------------|
| Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients – An Observational Study  |  |  |                      |                |                |  |   |   |      |      |               |                    |
| Methodology   | Population   | Intervention   |                      |                |                | Control  | Standard clinical practice                    | Limitations   |      |      |               |                    |
|   |  | A  | B                    | C              | D              |  |   |   |      |      |               |                    |
| Retrospective observational cohort study, 1/03/2020 - 22/04/2020, continuation until 05/05/2020   | N=2512<br>Women: 62%<br>Median age: 64 (IQR 52:76)<br><br>Patients diagnosed with PCR-confirmed COVID-19, hospitalised from 01/03/2020 to 05/05/2020.<br><br>Pregnant women participating in randomised trials who died on the first day of hospitalisation or were discharged within 24 hours were not included in the analysis<br><br>Average BMI: 27.6±5.5<br>Obesity: 41%<br>Hypertension: 55%<br>Diabetes: 32%<br>Coronary artery disease: 16%<br>COPD/asthma: 15%<br>Tumour: 12%<br>3 and more chronic conditions: 31% | HCQ<br>Na= 441   | HCQ+AZM<br>Nb= 1,473 | AZM<br>Nc= 256 | TOC<br>Nd= 198 | No HCQ/CQ<br>Nk1= 342<br><br>No TOC<br>Nk2=413 | in Poland – no established COVID-19 procedure | - No specific dosage information for individual patients;<br>- pre-print<br>- Lack of access to full data from the conducted study;<br>- observational nature of the study; |      |      |               |                    |
|   |  | HCQ dosage 80% of patients:<br>Day 1: 800 mg<br>Days 2-5: 400 mg<br><br>Median HCQ intake: 5 (IQR 4:5) |                      |                |                |  |   |   |      |      |               |                    |
| Results   |  |  |                      |                |                |  |   |   |      |      |               |                    |
| Endpoint  | Average hospitalisation duration (days)  | Intervention   |                      |                |                | Control  | HR (95% CI)                                   |   |      |      | NNH (95% CI)^ | Clinical relevance |
|   |  | A  | B                    | C              | D              |  | AvsK  | BvsK  | CvsK | DvsK |               |                    |
| Mortality for A, B, C (%)   | 30   | 25   | 18                   | 20             |                | 20   | 0.99 (0.80;1.22)^                             |   |      |      |               |                    |
| Mortality for D (%)   | 30   |  |                      |                | 46             | 56   | 0.76 (0.57;1.0)                               |   |      |      |               |                    |
| There were no statistically significant differences in the comparison of HCQ+/-AZM with no HCQ. The results for HCQ as monotherapy and HCQ+AZM are very similar. The authors of the study indicate it is impossible to draw conclusions on the efficacy of HCQ based on the above-mentioned data but are of the opinion that the results for TOC indicate a favourable trend. |  |  |                      |                |                |  |   |   |      |      |               |                    |

^Adjusted result

**Table 30. Description of the methodology and results of Rosenberg 2020 – hydroxychloroquine, azithromycin**

| Rosenberg 2020  |  |   |   |   |   |   |  |              |                    |
|---|--|---|---|---|---|---|--|--------------|--------------------|
| Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State |  |   |   |   |   |   |  |              |                    |
| Methodology   | Population   | Intervention 1  | Intervention 2  | Intervention 3  | Control   | Standard clinical practice                    | Limitations  |              |                    |
| Retrospective multi-centre study<br>Patients registered in New York between 15 and 28 March 2020 until 24 April                         | N=1438<br>Men: 59.7 %<br>Median age=63 years<br>Hospitalised patients with laboratory-confirmed COVID-19 | HCQ+AZM<br><br>N=735 (51.1%)<br>HCQ p.o. 200-600 mg 1x1 or 1x2 /day<br>AZM–p.o./ i.v. 200-500 mg 1x1 or 1x2/day | HCQ<br><br>N=271 (18.8%)<br><br>Dosage as in intervention 1 | AZM<br><br>N=211 (14.7%)<br><br>Dosage as in intervention 1 | ND – neither drug<br>Neither HCQ nor AZM was used<br>N=221 (15.4%)<br>Patients usually received i.a. lisinopril and ASA | in Poland – no established COVID-19 procedure | <ul style="list-style-type: none"><li>• Rapid transfer of patients to the ICU and mechanical ventilation was most often associated with administration of HCQ and AZM, which means that the results are not reliable in terms of efficacy assessment;</li><li>• Dosing information is accumulated in a manner which makes it impossible to identify the total daily dose in individual patients;</li><li>• Only in-hospital deaths were recorded, survival of patients discharged from the hospital was not monitored;</li><li>• Adverse events/effects were reported throughout the entire hospitalisation period, without distinguishing whether they occurred before or after treatment;</li><li>• Transferring patients from one hospital to another may not have been reported.</li></ul> |              |                    |
|   | Percentage of patients over 65 years of age (%)  | 43.8  | 50.6  | 46.5  | 46.2  |   |  |              |                    |
|   | Percentage of patients with diabetes (%)   | 36.6  | 41.7  | 27.5  | 29.0  |   |  |              |                    |
|   | Percentage of patients with hypertension (%)   | 58.0  | 59.8  | 50.7  | 54.8  |   |  |              |                    |
|   | Percentage of patients with dementia (%)   | 4.8   | 7.0   | 7.6   | 10.4  |   |  |              |                    |
|   | Percentage of patients with any chronic lung disease   | 17.6  | 25.1  | 18.0  | 10.9  |   |  |              |                    |
|   | Percentage of patients with any cardiovascular disease   | 29.1  | 36.5  | 25.6  | 32.1  |   |  |              |                    |
|   | Percentage of obese patients – BMI ≥30 (%)   | 46.6  | 41.5  | 39.3  | 30.0  |   |  |              |                    |
|   | Percentage of patients with abnormal chest imaging results (%)^  | 95.0  | 88.6  | 82.0  | 55.2  |   |  |              |                    |
| Results   |  |   |   |   |   |   |  |              |                    |
| Endpoint  |  | Observation period  | HCQ+AZM   | HCQ   | AZM   | ND  | OR (CI 95%)  | NNT (CI 95%) | Clinical relevance |
| Deaths (total percentage in the study = 20.3%) (%)  |  |   | 25.7  | 19.9  | 10.0  | 12.7  | -  | -            |                    |

| Rosenberg 2020  |                     |      |      |      |      |                     |            |  |
|---|---------------------|------|------|------|------|---------------------|------------|--|
| Cardiac arrest (%)  | 15/03/2020-24/04/20 | 15.5 |      |      | 6.8  | 2.13 (1.12; 4.05)*# | 12 (8; 23) |  |
| Abnormal ECG (defined as arrhythmia or QT prolongation) (%)   |                     | 27.1 | 27.3 | 16.1 | 14.0 | -                   | -          |  |
| Cardiac arrest in population which did not require mechanical ventilation (%)   |                     | -    | -    | -    | -    | 3.01 (1.07; 8.51)## | -          |  |
| <b>Authors' conclusions:</b> HCQ+AZM treatment or HCQ and AZM used as monotherapy, compared to treatment without HCQ or AZM, showed no statistically significant differences in terms of mortality. Interpretation of results is limited due to the study's observational nature.<br><b>The study was found that 65 years of age or older, cancer, kidney disease, cardiovascular disease, diabetes, abnormal chest imaging results, O2 saturation below 90%, low blood pressure, elevated creatinine and AST were statistically significantly associated with monitored endpoints.</b> |                     |      |      |      |      |                     |            |  |

\* Result adjusted for gender, age category (<65 vs 65 years), diabetes, any chronic lung disease, cardiovascular disease, abnormal chest imaging, respiration rate >22/min, O2 saturation <90%, increased creatinine and AST>40U/L as fixed effects and repeated measurements for the hospital; # Result for HCQ + AZM vs ND; ## results for HCQ vs AZM, statistically significant, no results for individual arms; ^defined as abnormal results of x-rays, magnetic resonance imaging and/or computed tomography at any time point during hospitalisation.

**Table 31. Description of the methodology and results of Huang 2020b – chloroquine**

| Huang 2020  |   |  |                    |   |  |                    |
|---|---|--|--------------------|---|--|--------------------|
| Preliminary evidence from a multicentre prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19   |   |  |                    |   |  |                    |
| Methodology   | Population  | Intervention                           | Control            | Standard clinical practice                    | Limitations  |                    |
| Prospective observational multi-centre study (11 centres), historically controlled<br><br>01/02/2020-08/03/2020   | N=373<br>Women: 62%<br>Median age: 43 (IQR 33:55)<br><br>Adult patients diagnosed with COVID-19 | CQ<br>Ni=197<br>500 mg p.o. 1x1 or 2x1 | No CQ<br>Nk=176    | in Poland – no established COVID-19 procedure | <ul style="list-style-type: none"><li>- pre-print</li><li>- historically controlled</li><li>- retrospective nature of the study</li><li>- short observation period</li></ul> |                    |
|   | Patients in moderate* condition %   | 93                                     | 89                 |   |  |                    |
|   | Women %   | 51                                     | 55                 |   |  |                    |
|   | Median age  | 43 (IQR 33:55)                         | 47.5 (IQR 35.8:56) |   |  |                    |
|   | Hypertension %  | 17                                     | 17                 |   |  |                    |
|   | Diabetes  | 5                                      | 8                  |   |  |                    |
| Results   |   |  |                    |   |  |                    |
| Endpoint  | Observation period (days)   | Intervention                           | Control            | Relative Difference/RR (95% CI)               | NNH (95% CI)^  | Clinical relevance |
| Time until virus is not detectable (median days (IQR))**  | 14  | 3.0<br>(3.0; 5.0)                      | 9.0<br>(6.0; 12.0) | Difference=-6(-6.0; -4.0)                     |  |                    |
| Number of patients with no virus detected   | 10  | 91                                     | 57                 | 1.43 (1.1; 1.85)^                             | 8 (5; 26)^   |                    |
|   | 14  | 96                                     | 80                 | 1.07 (0.86; 1.33)                             |  |                    |
| Any adverse event   | 14  | 26.9                                   | 32.4               | 0,83 (0.61; 1.14)                             |  |                    |
| The results of the study indicate a shorter median time to reaching a point where the virus was undetectable in patients in the CQ population. At the same time, a statistically significant difference was noted in favour of the CQ arm in comparison to the control arm, in terms of achieving the moment of the virus not being detectable in patients. There were no statistically significant differences in the occurrence of any adverse event. The authors of the publication indicate the need to continue research on the safety and efficacy of CQ used in treatment of COVID-19. |   |  |                    |   |  |                    |

\* fever, respiratory symptoms, changes in imaging indicating pneumonia; ^Agency's own calculations; \*\*its definition is uncertain

**Table 32. Description of the methodology and results of Saleh 2020 – chloroquine, hydroxychloroquine**

| Saleh 2020   |  |  |  |   |  |              |                    |
|--|--|--|--|---|--|--------------|--------------------|
| The Effect of Chloroquine, Hydroxychloroquine and Azithromycin on the Corrected QT Interval in Patients with SARS-CoV-2 Infection  |  |  |  |   |  |              |                    |
| Methodology  | Population   | Intervention A   | Intervention B   | Standard clinical practice                    | Limitations  |              |                    |
| Prospective, observational<br>Multi-centre (3 centres)<br><br>01/03/2020-23/03/2020<br><br>United States   | N=201<br>Men: 57.2%<br>Average age:58.5 ± 9.1<br>Adult patients with COVID-19 confirmed by PCR<br>Average QRS duration: 92.8 ± 19.0 ms<br>Average QTc value: 439 ± 24.8<br>QTc > 500 ms – 8 patients (4%)<br>Hypertension: 60.2%<br>Diabetes: 32.3%<br>Coronary artery disease: 11.4%<br>COPD/asthma: 14.9%<br>Use of drugs prolonging the QT segment: 40.3% | CQ<br>Ni1=10<br>Day 1: 500mg 2x1<br>Days 2-5: 500 mg 1x1 | HCQ<br>Ni2=191<br>Day 1: 400 mg 2x1<br>Days 2-5: 200 mg 2x1<br><br>119 patients also used AZM<br>Days 1-5: 500 mg i.v. | in Poland – no established COVID-19 procedure | <ul style="list-style-type: none"><li>• No control arms where CQ or HCQ were not used</li><li>• Observational nature of the study</li><li>• Small population size</li><li>• Short observation period</li></ul> |              |                    |
| Results  |  |  |  |   |  |              |                    |
| Endpoint   |  | Observation period (days)                                | Intervention A   | Intervention B                                | OR (CI 95%)  | NNT (CI 95%) | Clinical relevance |
| QT prolongation resulting in TdP   |  | 22   | 0  | 0   |  |              |                    |
| QT prolongation resulting in discontinuation of CQ/HCQ+/-AZM (%)   |  |  | 3.5  |   |  |              |                    |
| Death from arrhythmia  |  |  | 0  | 0   |  |              |                    |
| New atrial fibrillation %  |  |  | 8.5  |   |  |              |                    |
| Unstable monomorphic ventricular tachycardia %   |  |  | 3.5  |   |  |              |                    |
| Persistent monomorphic ventricular tachycardia %   |  |  | 0.5  |   |  |              |                    |
| No TdP, which was considered the primary endpoint, was noted in the study. Rare cases of discontinuation associated with QT prolongation were reported. Due to its nature and limitations, the study does not allow for drawing clear conclusions on its basis |  |  |  |   |  |              |                    |

#### 2.1.1.5. Remdesivir

| <b>Recommendation</b>   |
|---|
| In the absence of confirmed efficacy data, routine use of remdesivir is not recommended; its use should be restricted to clinical trials. |

**Justification:**

Five scientific reports assessing the efficacy and safety of remdesivir were identified. Grain 2020<sup>173</sup> is an analysis of the results of patients treated with remdesivir in the *compassionate use* mode.

Holshue 2020<sup>174</sup>, Kujawski 2020<sup>175</sup> [preprint], Lescure 2020 and Hillaker 2020<sup>176</sup> constitute descriptions of individual patients or series of patients treated with remdesivir. The patients described in the above-mentioned studies were included in the analysis presented in Grain 2020 (see table below).

**Table 33. Description of the methodology and results of Grein 2020 – remdesivir**

| Grein 2020 <sup>177</sup>  |  |  |  |   |
|--|--|--|--|---|
| Methodology  | Population / endpoint  | Observation time   | Intervention   | Clinical relevance  |
| Retrospective study<br>- <i>compassionate use</i> .<br>Patients: USA (n=22); Italy (n=12), Austria (n=1), France (n=4), the Netherlands (n=2), Spain (n=1), Canada (n=1) and Japan (n=9). Treatment: from 25/01/2020 to 07/03/2020. Observation for at least 28 days from the start of treatment or until discharge or death.  | N=53<br>Age (median): 64 (range 23-82), 75% were men   |  | Remdesivir<br>- 40 (75%) patients received the full 10-day treatment;<br>- 10 (19%): 5-9 days of treatment;<br>- 3 (6%): <5 days of treatment.<br>10-day treatment cycle: 200 mg i.v. 1st day, then 100mg/day for 9 days.  | Current clinical practice: in Poland – no established COVID-19 procedure      |
|  | Inclusion criteria: blood saturation at ≤94% when breathing air or oxygen; creatinine clearance at <30 mL/min; ALT and AST – less than 5x the upper limit of the norm; consent to refrain from taking other experimental drugs<br>Prior to the start of the therapy, 34 (65%) required invasive ventilation, of which 30 (57%) required mechanical ventilation and 4 (8%) required ECMO<br>Median time of pre-treatment symptoms: 12 days. |  |  |   |
| Limitations:<br>- retrospective analysis of the results of patients treated in various centres<br>- possible errors in reporting individual results;<br>- varied baseline patient characteristics;<br>- no control group,<br>- small sample size;<br>- non-uniform duration of remdesivir use;<br>- no data for 8 patients;<br>- short observation period;<br>- commercial sponsor: Gilead | Improvement / deterioration in respiratory efficiency assessed on the basis of oxygen supplementation  | Median: 18 days (IQR: 13;23)   | Improvement: 36/53 (68%);<br>Deterioration: 8/53 (12%);<br>Improvement:<br>- 12/12 (100%) air-breathing or low-flow oxygen therapy;<br>- 5/7 (71%), non-invasive ventilation<br>- 17/30 (57%) extubated, mechanically ventilated patients<br>- 3/4 (75%); ECMO was discontinued. | -   |
|  | Deaths   |  | 7/53(13%)<br>- 18% (6/34) invasively ventilated<br>- 5% (1 /19) of the remaining patients  | Hard endpoint. Lack of control group does not allow for assessing the result. |
|  | Discharge from hospital [days from the start of treatment]   | Within 44 days   | 25/53 (47%)  | High uncertainty of estimations.<br>Frequent and serious adverse events.      |
|  | Cumulative clinical improvement percentage * - Kaplan-Meier analysis [from the start of treatment]   | Up to 28 days  | 84% (95%CI: 70–99)   |   |
|  | Adverse events of any type   | During at least 28 days from the start of treatment or until discharge or death. | 32/53 (60%): Most frequently: elevated liver enzymes (12/53, 23%), diarrhoea (5/53, 9%), rash (4/53, 8%), renal impairment (4/53, 8%) and hypotension (4/53, 8%).  |   |
|  | Serious adverse events   |  | 12/53 (23%): Most frequently: multiple organ dysfunction syndrome (2/53, 4%); septic shock (2/53, 4%); acute renal failure (2/53, 4%), hypotension (2/53, 4%) – all in invasively ventilated patients.   |   |
|  | Discontinuation of remdesivir treatment  |  | 4/53 (8%): one due to deteriorating renal failure, one due to multiple organ dysfunction syndrome, 2 due to elevated transaminases,  |   |
| Conclusions: In the absence of a control group, it is impossible to assess whether remdesivir is of any benefit to patients receiving it. The frequency of adverse effects (60%), including severe adverse effects (23%) is not low and the possibility that remdesivir brings more harm than benefits cannot be underestimated. The study result is inconclusive.                         |  |  |  |   |

\* improvement defined as a reduction of the result by 2 points or more compared to the state at the start of treatment assessed on a 6-point scale (from 1 – discharged from hospital, to 6 – death)

**Table 34. Description of the methodology and results of Wang 2020<sup>178</sup> – remdesivir**

| Wang 2020   |   |  |  |   |   |                    |
|---|---|--|--|---|---|--------------------|
| Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multi-centre trial |   |  |  |   |   |                    |
| Methodology   | Population  | Intervention   | Control  | Standard clinical practice                  | Limitations   |                    |
| RCT<br>multi-centre<br>double-blind;<br>06/02/2020 –<br>12/03/2020<br><br>China                               | N=237<br>Age: 65 (IQR: 56-71)<br><u>Inclusion criteria:</u> hospitalised patients aged ≥ 18 years old; PCR-confirmed SARS-CoV-2; imaging-confirmed pneumonia; blood saturation at ≤94% when breathing air; oxygenation index <300 mmHg; onset of symptoms within 12 days of inclusion.<br><u>Exclusion criteria:</u> pregnancy and breastfeeding; ALT and AST – above 5x standard; cirrhosis; severe renal failure, renal replacement therapy – haemodialysis or peritoneal dialysis. | RDV<br>Ni=158<br><br>Remdesivir (RDV)<br>Day 1 – RDV 200 mg i.v.<br>Day 2-10 – RDV 100 mg/day i.v. | PLC<br>Nk=78<br><br>Treatment cycle: in line with the intervention | No established COVID-19 procedure in Poland | - early discontinuation of the study, which reduced the number of patients included in the analysis. As a result, the statistical power of the study was insufficient to demonstrate clinical differences between the studied arms;<br>- no data on the number of patients tested negative for the virus; |                    |
|   | Men   | 56%  | 65%  |   |   |                    |
|   | Co-morbidities (hypertension, diabetes, myocardial ischaemia)   | 71%  | 71%  |   |   |                    |
|   | Use of alpha2b interferon   | 29%  | 38%  |   |   |                    |
|   | Use of lopinavir/ritonavir  | 28%  | 29%  |   |   |                    |
| Results   |   |  |  |   |   |                    |
| Endpoint  | Therapy period (days)   | Intervention   | Control  | Relative parameter<br>HR/RR (95% CI)        | Absolute parameter  | Clinical relevance |
| Median time to clinical improvement^  | 28  | total  |  | HR=1.23 (0.87; 1.75)                        |   |                    |
|   |   | 21 (IQR:13–28)   | 23 (IQR:15-28)   |   |   |                    |
|   |   | Administration ≤10 days after onset of symptoms  |  | HR=1.52 (0.95; 12.43)                       |   |                    |
|   |   | 18·(IQR:12–28)   | 23·(IQR:15–28)   |   |   |                    |
|   |   | Administration >10 days after onset of symptoms  |  | HR=1.07 (0.63; 1.83)                        |   |                    |
| 23 <sup>#</sup>   |   | 24 <sup>#</sup>  |  |   |   |                    |
| Clinical improvement (%)  |   | 65   | 58   | RR=1.13 (0.91; 1.41)                        |   |                    |
| Death %   |   | Total  |  | RR=1.09 (0.54; 2.18)                        |   |                    |
|   |   | 14   | 13   |   |   |                    |
|   |   | Administration ≤10 days after onset of symptoms  |  | RR=0.76 (0.29; 1.95)                        |   |                    |
|   |   | 11   | 15   |   |   |                    |

| Wang 2020  |  |   |    |                                    |  |
|--|--|---|----|------------------------------------|--|
|  |  | Administration >10 days after the onset |    | RR=1.48 (0.45; 4.88)               |  |
|  |  | 14                                      | 10 |                                    |  |
| Discharge (%)  |  | 58                                      | 58 | RR <sup>\$</sup> =1.01 (0.8; 1;27) |  |
| The analysis indicates no statistically significant differences in the occurrence of: any adverse events, any grade 3-4 adverse events, any severe adverse events and any adverse events resulting in treatment discontinuation. 155 patients were included within the safety framework.   |  |   |    |                                    |  |
| <b>The use of RDV did not result in statistically significant differences between the intervention and control arms. It should be noted that the study was discontinued before the scheduled date, which limits the possibility of drawing conclusions on the lack of efficacy or on a similar RDV safety profile compared to the PLC.</b> |  |   |    |                                    |  |

^improvement defined as the time (days) from randomisation to a reduction of the result by 2 points or more in comparison with the baseline condition assessed on a 6-point scale (from 1 – discharged from the hospital, to 6 – death) or being discharged from the hospital; \$ – Agency's own calculations; # no data

**Table 35. Description of the methodology and results of Beigel 2020 – remdesivir**

| Beigel 2020   |   |   |              |   |  |   |  |   |
|---|---|---|--------------|---|--|---|--|---|
| Remdesivir for the Treatment of Covid-19 – Preliminary Report   |   |   |              |   |  |   |  |   |
| Methodology   |   | Population  |              | Intervention  | Control  | Standard clinical practice                    | Limitations  |   |
| <p>RCT, double-blind, phase III multi-centre study,<br/>Study time:<br/>21/02/2020 – 19/04/2020<br/>Randomisation 1:1</p> <p>Stratification by place of conducting the study and severity of the disease at the time of inclusion in the study was included<br/>The patient's clinical condition was monitored daily using an 8-point sequential scale ^ and NEWS<sup>a</sup></p> |   | N=1,063, of which 1,059 were analysed   |              | Ni= 541 of which 538 were analysed  | Nk=522 of which 521 were analysed                        | In Poland – no established COVID-19 procedure | <p>–the publication includes only preliminary results of the ACTT-1 study, which is related to the value of the information collected to date;</p> <p>–originally, a difference in clinical condition based on an 8-point sequential scale was assumed to be the primary endpoint, in patients receiving RDV compared to PLC on day 15.</p> <p>–the use of best supportive care was allowed in accordance with hospital policy or adopted guidelines, but it was not possible to use therapies considered experimental in patients from day 1 to 29. Still, it should be borne in mind that such a therapy may have been used before inclusion in the study;</p> <p>–short observation period, which may have not been sufficient to allow recovery of some patients</p> |   |
|   |   | Patients with laboratory-confirmed COVID-19<br>Age: 58.9±15.0<br>Men: 64.3%<br>Co-morbidities:<br>1 disease – 27.0%<br>≥ 2 diseases – 52.1%<br>hypertension (49.6%),<br>obesity (37.0%),<br>type 2 diabetes (29.7%) |              | Remdesivir (RDV):<br>1. day – 200 mg i.v. 1x1<br>2-10 day – 100 mg i.v. 1x1 (or until discharge or death)<br>+ best supportive care | PLC: dosing regimen as for RDV<br>+ best supportive care |   |  | 53 people – treatment discontinuation before day 10 (AE or SAE other than death – 36; consent withdrawal – 15; disqualification from the study – 2; |
|   |   | 4 11.9  |              | 12.4  | 11.5   |   |  |   |
|   |   | 5 39.6  |              | 41.0  | 38.1   |   |  |   |
|   |   | 6 18.5  |              | 18.1  | 19.0   |   |  |   |
| 7 25.6  |   | 23.1  | 28.2         |   |  |   |  |   |
| Percentages of patients with individual assessments on an 8-point scale* (%)  |   |   |              |   |  |   |  |   |
| Results   |   |   |              |   |  |   |  |   |
| Endpoint  |   | Observation period (days)   | Intervention | Control   | RR/HR parameter (95% CI)                                 | NNT/ NNTH parameter (95% CI)                  | Clinical relevance   |   |
| Cured <sup>1</sup>  | General population                      | 28  | 334/538      | 273/521   | RR=1.32 (1.12; 1.55) <sup>^</sup>                        | NNH=11(7;27) <sup>^^</sup>                    |  |   |
|   | Population with a score of 4 (baseline) |   | 61/67        | 47/60   | RR=1.38 (0.94; 2.03) <sup>^</sup>                        |   |  |   |
|   | Population with a score of 5 (baseline) |   | 177/222      | 128/199   | RR=1.47 (1.17; 1.84) <sup>^</sup>                        | NNH=7(5;15) <sup>^^</sup>                     |  |   |
|   | Population with a score of 6 (baseline) |   | 47/98        | 43/99   | RR=1.20 (0.79; 1.81) <sup>^</sup>                        |   |  |   |
|   | Population with a score of 7 (baseline) |   | 45/125       | 51/147  | RR=0.95 (0.64; 1.42) <sup>^</sup>                        |   |  |   |
| Death   | General population                      | 14  | 32/538       | 54/521  | HR=0.70 (0.47;1.04) <sup>^</sup>                         | NNT=23 (89;13) <sup>^^</sup>                  |  |   |
|   | Population with a score of 4 (baseline) |   | 1/67         | 1/60  | HR=0.46 (0.04; 5.08) <sup>^</sup>                        |   |  |   |
|   | Population with a score of 5 (baseline) |   | 4/222        | 19/199  | HR=0.22 (0.08; 0.58) <sup>^</sup>                        | NNT=13 (31;9) <sup>^^</sup>                   |  |   |

| Beigel 2020  |   |  |         |         |                              |                          |
|--|---|--|---------|---------|------------------------------|--------------------------|
|  | Population with a score of 6 (baseline) |  | 13/98   | 13/99   | HR=1.12 (0.53; 2.38)^        |                          |
|  | Population with a score of 7 (baseline) |  | 13/125  | 19/147  | HR=1.06 (0.59; 1.92)^        |                          |
| Serious adverse events   |   |  | 114/541 | 141/522 | <b>RR=0.78 (0.63; 0.97)^</b> | <b>NNT=17 (124; 10)^</b> |
| Respiratory failure  |   |  | 28/541  | 42/522  | RR=0.64 (0.4; 1.02)^         |                          |
| The remaining safety endpoints did not indicate statistically significant differences between the arms. Acute respiratory failure, hypotension, pneumonia and acute renal failure occurred slightly more frequently in the PLC arm. Two events in both arms were classified as treatment-related adverse events.   |   |  |         |         |                              |                          |
| <b>The authors' conclusions demonstrate the advantage of a 10-day treatment cycle with remdesivir over placebo in terms of shortening the recovery time of hospitalised adults diagnosed with COVID-19. At the same time, it should be borne in mind that the study has not been completed yet. The results were the most satisfactory in patients who scored 5 on the 8-point scale (hospitalised patients requiring oxygen ventilation). However, it is worth mentioning that failure to demonstrate statistically significant differences in the remaining arms may be associated with a lower population size than in the arm assessed at 5 points. In addition, the observation period may have been too short for a part of the subpopulation, especially taking into account the definition of recovery as an assessment of 1, 2 or 3 on the 8-point scale. Additionally, the authors of the study underline the necessity to start antiviral therapy before progression of respiratory failure leading to the necessity of using mechanical ventilation.</b> |   |  |         |         |                              |                          |

1. Defined as the first day in the 28 days after inclusion in the study, when the patient met the category 1, 2 or 3 on an \*8-point scale (where 1 – patient is not hospitalised, no limitation of activities, 2 – without hospitalisation, with limitations, 3 – hospitalisation without existing medical problems, 4 – hospitalisation without oxygen supply, 5 – hospitalisation with oxygen ventilation, 6 – hospitalisation with the need to supply significant amounts of oxygen, without invasive mechanical ventilation, 7 – hospitalisation with mechanical ventilation or ECMO, 8 – death); ^Results after stratification in the Cox model; & *National Early Warning Score*

**Table 36. Description of the methodology and results of Goldman 2020 – remdesivir**

| Goldman 2020   |   |   |  |   |  |   |  |
|--|---|---|--|---|--|---|--|
| Remdesivir for 5 or 10 Days in Patients with Severe Covid-19   |   |   |  |   |  |   |  |
| Methodology  | Population  |   | Intervention I   | Intervention II   | Standard clinical practice                     | Limitations   |  |
| Multi-centre, phase III, open RCT without stratification,<br><br>Randomisation 1:1<br><br>Duration of the study: 06/03/2020-26/03/2020<br><br>Both arms in the course of RDV treatment continued to be treated at the researcher's discretion throughout the entire course of the study.<br><br>55 hospitals (USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan) | N= 397<br>Patients with laboratory-confirmed SARS-CoV-2 infection   |   | N <sub>1</sub> = 200<br><br>RDV – 5 days<br>1. day – 200 mg i.v. 1x1<br>2-5 day – 100 mg i.v.1x1<br><br>172 patients completed a 5-day cycle of RDV treatment, 16 were discharged from the hospital. | N <sub>2</sub> = 197<br><br>RDV – 10 days<br>1. day – 200 mg i.v. 1x1<br>2-10 day – 100 mg i.v. 1x1<br><br>86 patients completed a 10-day cycle of RDV treatment, 68 were discharged from hospital earlier, 22 did not complete treatment due to AEs, 12 patients died. | in Poland<br>no established COVID-19 procedure | – no control arm<br>– open-label study<br>– one of the primary endpoints was changed in the course of the study: the percentage of patients with temperature normalisation on day 14 was replaced by evaluation of the clinical condition on a 7-point scale on day 14.<br>– the protocol was changed by adding an extended phase of the study and 5,600 additional patients, including a cohort of patients with mechanical ventilation (results not presented in the publication)<br>– in the RDV arm, only 44% of patients completed the full treatment cycle<br>– no results of the viral load during and after treatment |  |
|  | <u>Inclusion criteria:</u> patients aged ≥12 years old (change in protocol from 18 years old); SARS-CoV-2 infection confirmed by RT-PCR within 4 days before randomisation; pulmonary infiltrates confirmed by x-ray; SpO <sub>2</sub> ≤94% during spontaneous breathing or receiving additional oxygen<br><u>Exclusion criteria:</u> Patients using mechanical ventilation/ECMO; patients with symptoms of multi-organ failure; ALT and AST levels >5-times the upper limit of normal creatinine clearance < 50mL/min; patients receiving other treatment with possible activity against COVID-19 (within 24 hours before initiation of trial treatment) |   |  |   |  |   |  |
|  | Age (IQR)   |   | 61 (IQR 50-69)   | 62 (IQR 50-71)  |  |   |  |
|  | Men %   |   | 60   | 68  |  |   |  |
|  | Output vs final percentages of patients with individual scores on a 7-point sequential scale*%  | 2 | 2 vs 8   | 5 vs 17   |  |   |  |
|  |   | 3 | 24 vs 4  | 30 vs 5   |  |   |  |
|  |   | 4 | 56 vs 10   | 54 vs 7   |  |   |  |
|  |   | 5 | 17 vs 6  | 11 vs 7   |  |   |  |

| Results  |                           |                     |                      |                               |                    |                    |
|--|---------------------------|---------------------|----------------------|-------------------------------|--------------------|--------------------|
| Endpoint   | Observation period (days) | 5-day RDV treatment | 10-day RDV treatment | Relative parameter (95% CI)** | NNT/ NNTH (95% CI) | Clinical relevance |
| Time to achieving clinical improvement of min. 2 points on a 7-point scale % | 14                        | 10 days (IQR 6-18)  | 11 days (IQR 7-18)   | HR=0.79 (0.61; 1.01)          |                    |                    |
| Clinical improvement of min. 2 points on a 7-point scale %                   | 5                         | 16                  | 15                   | RD= 0.2% (-7.0; 7.5);         |                    |                    |
|  | 7                         | 36                  | 27                   | RD= -5.0% (-14.0; 4.0);       |                    |                    |

| Goldman 2020   |    |                    |                    |                         |  |  |
|--|----|--------------------|--------------------|-------------------------|--|--|
|  | 11 | 64                 | 49                 | RD= -4.8% (-14.1; 4.6); |  |  |
|  | 14 | 65                 | 54                 | RD= -6.5% (-15.7; 2.8); |  |  |
| Time to recovery^^%  | 14 | 10 days (IQR 6-18) | 11 days (IQR 7-18) | HR=0.81 (0.64; 1.04)    |  |  |
| Hospitalisation length of discharged patients %  |    | 7 days (IQR 6-10)  | 8 days (IQR 5-10)  |                         |  |  |
| Discharged patients%   |    | 60                 | 52                 |                         |  |  |
| Death %  |    | 8                  | 11                 |                         |  |  |
| Serious adverse events in total%   |    | 21                 | 35                 |                         |  |  |
| Treatment discontinuation due to AEs %   |    | 4                  | 10                 |                         |  |  |
| <b>The authors' conclusions suggest that remdesivir therapy may have a positive effect on pneumonia resulting from a SARS-CoV-2 infection, especially in non-critical patients. The authors indicate that remdesivir has been used in the study as part of the so-called "compassionate use", while at the same time underlining the need to conduct randomised control trials to determine the safety and efficacy of remdesivir in the treatment of SARS-CoV-2 infections.</b> |    |                    |                    |                         |  |  |

\* A scale indicating deterioration or improvement of the hospitalised patient's condition (1 – death; 2 – hospitalised patient, undergoing invasive mechanical ventilation or ECMO; 3 – a hospitalised patient undergoing non-invasive ventilation or high-flow oxygen devices; 4 – hospitalised patient requiring low-flow oxygen supplementation treatment; 5 – hospitalised patient not requiring oxygen but receiving continuous medical care (related or unrelated to COVID-19); 6 – hospitalised patient, not requiring additional oxygen or continuous medical care (other than that specified in the protocol for the administration of remdesivir); 7 – non-hospitalised patient. \*\* in relation to the baseline clinical condition; ^^ Recovery is defined as an improvement in the sequential scale from a baseline score of 2-5 to score 6 or 7.

**Table 37. Description of the methodology and results of Antinori 2020 – remdesivir**

| Antinori 2020  |  |  |                     |   |  |                    |
|--|--|--|---------------------|---|--|--------------------|
| Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post-treatment hospitalisation status   |  |  |                     |   |  |                    |
| Methodology  | Population   | Intervention   | Control             | Standard clinical practice                  | Limitations  |                    |
| Prospective, open, single-centre study, type “compassionate use”<br><br>Duration of the study: 23/02 – 20/04/2020<br>Goal: to assess the safety and efficacy of remdesivir in the treatment of patients with severe pneumonia caused by a SARS-CoV-2 infection | N=35<br>Men: 74.3%<br>ICU vs IDU (Infectious Disease Unit) patients 18/35 vs 1735<br>Median age: 63.0 (IQR 51.0:69.0)<br><br>Inclusion criteria: Patients with pneumonia (confirmed by chest X-ray or CT scan) caused by RT-PCR-confirmed SARS-CoV-2, ≥18 years old, undergoing mechanical ventilation or with saturation ≤94%, or NEWS2 score ≥4.<br><br>Exclusion criteria: ALT or AST >5 times the upper limit of normal, creatinine clearance <30 mL/min | Ni=35<br><br>Remdesivir (RDV)<br>Day 1 – RDV 200 mg i.v.<br>Day 2-10 – RDV 100 mg/day i.v.<br><br>31/35 patients previously treated with LPV/RTV + HCQ (median: 5 days)<br><br>13/35 (37%) of patients did not complete the 10-day RDV treatment, of which 8/35 (22.8%) due to adverse events. | -                   | in Poland no established COVID-19 procedure | - no control arm;<br>- limited population size<br>- compassionate use study<br>- the majority of patients previously received LPV / RTV + HCQ, which may interfere with the analysis of RDV efficacy;<br>- no possibility to predefine the period of viral observation |                    |
| Results  |  |  |                     |   |  |                    |
| Endpoint   | Therapy period (days)  | Patients in the ICU  | Patients in the IDU | Relative parameter                          | Absolute parameter   | Clinical relevance |
| Change in the 7-point scale score* – death (%)   | 10   | 22.2   | 5.88                |   |  |                    |
|  | 28   | 44.4   | 5.88                |   |  |                    |
| Change in the 7-point scale score* – further invasive ventilation (%)  | 10   | 55.5   | -                   |   |  |                    |
|  | 28   | 16.7   | -                   |   |  |                    |
| Change in the 7-point scale score* – further high-flow therapy and/or non-invasive mechanical ventilation is necessary. (%)  | 10   | -  | 58.82               |   |  |                    |
|  | 28   | -  | 5.88                |   |  |                    |
| Change in the 7-point scale score* – improvement of hospitalisation status (%)   | 10   | 22.2   | 35.3                |   |  |                    |
|  | 28   | 38.9   | 88.2                |   |  |                    |
| Adverse events leading to treatment discontinuation  | -  | 33.3   | 11.7                |   |  |                    |
| Increase in transaminase level   | -  | 44.4   | 41.2                |   |  |                    |
| Acute nephritis  | -  | 38.8   | 5.9                 |   |  |                    |
| Increase in bilirubin level  | -  | 11.1   | 29.4                |   |  |                    |

**Antinori 2020**

**The authors' conclusions suggest that remdesivir treatment may have a positive effect on pneumonia resulting from a SARS-CoV-2 infection, especially in patients in non-critical condition. The authors indicate that remdesivir has been used in the study as part of the so-called "compassionate use", while at the same time underlining the need to conduct randomised control tests to determine the safety and efficacy of remdesivir in the treatment of SARS-CoV-2 infections.**

\* A scale indicating deterioration or improvement of the hospitalised patient's condition (1=non-hospitalised, returning to normal daily activities, 7=dead). The lower the score, the better the patient's condition. ^IDU – Infectious Disease Unit

#### 2.1.1.6. Favipiravir

| <b><i>Recommendation</i></b>   |
|--|
| In the absence of confirmed efficacy data, routine use of favipiravir is not recommended; its use should be restricted to clinical trials. |

***Justification:***

Two studies on the efficacy and safety of favipiravir in COVID-19 have been identified:

- Chen 2020, an RCT which compared favipiravir (FAV) to arbidol (ARB), is a pre-print which has not yet undergone the review process – Table 38;
- Cai 2020, an open controlled study which compared favipiravir therapy to lopinavir/ritonavir (L/R) therapy, is available as a pre-proof (the article has been reviewed) – Table 39.

**Table 38. Description of the methodology and results of Chen 2020 (pre-print) – favipiravir**

| Chen 2020 ( <i>pre-print</i> ) <sup>179</sup>  |  |                      |  |   |  |                  |  |  |
|--|--|----------------------|--|---|--|------------------|--|--|
| Study methodology  | Population / endpoint  | Observation time     | Intervention   | Control   | Relative parameter (95% CI, p value)                                     | NNT/NNH (95% CI) | Clinical relevance   |  |
| <b>RCT</b> <ul style="list-style-type: none"><li>multi-centre (3 centres: in the Wuhan region)</li><li>non-blinded</li><li>hypothesis: superiority</li><li>duration of the study: from 20 February 2020 to 12 March 2020</li></ul> | N= 236<br>Age:<br>< 65 years of age – 87 (75%) FAV and 79 (65.8%) ARB<br>≥ 65 years of age – 29 (25%) FAV and 41 (34.2%) ARB<br>Sex: FAV – 57 (49.1%) women, ARB – 69 (57.5%) women  |                      | Ni=116<br><br>FAV in tablet day 1: 1,600 mg 2 per day from day 2: 600 mg, 2 per day + standard therapy treatment 7-10 days | Nk=120<br><br>ARB 200 mg 3 per day + standard therapy + treatment 7-10 days | Current clinical practice: in Poland – no established COVID-19 procedure |                  |  |  |
|  | <ul style="list-style-type: none"><li><b>Inclusion criteria:</b> age ≥ 18 years old; onset of symptoms within 12 days of inclusion; COVID-19 pneumonia.</li><li><b>Exclusion criteria:</b> FAV or ARB allergy; ALT/AST exceeded 6 times; patients in severe/critical condition with a predicted life expectancy of &lt;48h; pregnant women; HIV infection.</li></ul> |                      |  |   |  |                  |  |  |
| Study limitations:<br>- observation time;<br>- differences in baseline characteristics: 18 (FAV) vs 9 (ARB) patients in critical condition; 54/116 in the FAV arm and 46/120 ARB were tested positive for the infection on day 0   | Recovery   | 7-10 days of therapy | 71/116.  | 62/120.   | RR = 1.18 (0.95; 1.48)   | N/A              | Clinically insignificant differences                                     |  |
|  | Recovery – patients with moderate symptoms   |                      | 70/98.   | 62/111.   | OR=1.28 (1.04; 1.57), p=0.02   | 7 (4; 37)*       |  |  |
|  | Recovery – patients in severe/critical condition   |                      | 1/18.  | 0/9.  | RR = 1.58 (0.07; 35.32)  | N/A              |  |  |
|  | Recovery – patients with diabetes and hypertension   |                      | 23/42.   | 18/35.  | RR = 1.06 (0.70; 1.63)   | N/A              |  |  |
|  | Need to include oxygen therapy or non-invasive mechanical ventilation (NMV)  |                      | 21/116.  | 27/120.   | RR = 0.8 (0.48; 1.34)  | N/A              |  |  |
|  | <b>Deaths from any cause</b>   |                      | <b>0/116.</b>  | <b>0/120.</b>   | -  | -                | <b>No differences</b>  |  |
|  | Dyspnoea after drug administration   |                      | 4/116.   | 14/120.   | OR=0.30 (0.10; 0.87), p=0.027  | 13 (7; 64)*      | Significantly more frequent dyspnoea following ARB                       |  |
|  | Respiratory failure  |                      | 1/116.   | 4/120.  | RR = 0.25 (0.03; 2.20)   | N/A              | The small number of events does not allow for assessing the differences. |  |
|  | Total adverse events   |                      | 37/116, 31.90%   | 28/120, 3.33%   | RR = 1.37 (0.90; 2.08)   | N/A              | -  |  |
|  | Increased uric acid levels   |                      | 16/116, 13.79%   | 3/120, 2.50%  | OR=5.52 (1.65; 18.44), p=0.006   | NDA              | -  |  |
|  | No statistically significant differences in the following adverse events: abnormal liver function tests, psychiatric reactions, gastrointestinal adverse events  |                      |  |   |  |                  |  |  |
|  | <b>Conclusions: Controlled medium-sized randomised clinical trial comparing Favipiravir with Arbidol. The choice of the comparator is not justified by the current practice – no reliable data on the efficacy and safety of using Arbidol in COVID-19 is available. The study did not demonstrate an advantage of any of the compared drugs.</b>                    |                      |  |   |  |                  |  |  |

^ data derived directly from the study; \*analysts' own calculations; \*\*recovery was defined as: ongoing (> 72 h) improvement in body temperature, number of breaths, saturation, resolution of cough, with the following quantitative criteria: body temperature ≤ 36.6°C, number of breaths ≤ 24/minute, saturation ≥ 98%, no oxygen support, moderate or no cough; abbreviations: FAV – favipiravir, ARB – arbidol, RR – relative risk; N/A – not applicable; NDA – no data available

**Table 39. Description of the methodology and results of Cai 2020 (pre-proof) – favipiravir**

| Cai 2020 (pre-proof) <sup>180</sup>   |   |   |  |  |                                      |              |                    |
|---|---|---|--|--|--------------------------------------|--------------|--------------------|
| Study methodology   | Population / endpoint   | Observation time  | Intervention   | Control  | Relative parameter (95% CI, p value) | NNT (95% CI) | Clinical relevance |
| Open controlled non-randomised clinical trial <ul style="list-style-type: none"><li>1 centre (<i>The Third People's Hospital of Shenzhen</i>)</li><li>Two arms: favipiravir (FAV) or lopinavir/ritonavir (LPV/RTV)</li><li>Patient inclusion period: FAV arm --from 30/01/2020 to 14/02/2020, LPV/RTV arm – from 24 to 30/01/2020 – afterwards, observation for 14 days</li></ul>   | Number of patients: 80 patients: FAV = 35; LPV/RTV = 45<br>Age of patients – median (IQR): FAV – 43 (35.5 – 59); LPV/RTV – 49 (36-61)<br>Sex: FAV – 35 (43.8%) men, LPV/RTV – 14 (40.0%) men<br>Treatment period: until tested negative for the virus or up to 14 days  | N= 35<br><br>FAV in tablet form (200 mg) <ul style="list-style-type: none"><li>day 1: 1,600 mg 2 per day</li><li>days 2-14: 600 mg 2 per day</li></ul> In addition, patients received IFN-α1b 60μg, 2 per day as inhalation spray | N=145<br><br>LPV/RTV (tablets: 200mg/50 mg) <ul style="list-style-type: none"><li>days 1-14: LPV 400 mg/ RTV 100 mg – 2 per day</li></ul> In addition, patients received IFN-α1b 60μg, 2 per day as inhalation spray | Current clinical practice:<br>No established COVID-19 procedure in Poland. |                                      |              |                    |
|   | Study population <ul style="list-style-type: none"><li><u>Inclusion criteria</u>: ages 16-75; test-confirmed presence of coronavirus infection; no more than 7 days between the onset of symptoms to the inclusion in the study; taking contraception during the study and 7 days after its completion; no difficulty swallowing tablets</li><li><u>Exclusion criteria</u>: severe clinical condition (meeting one of the following criteria: resting number of breaths per minute &gt;30, saturation &lt;93%, oxygenation index &lt;300 mmHg (1 mmHg = 133.3 Pa), respiratory failure, shock and/or presence of other organ failure requiring monitoring and ICU treatment); chronic liver and kidney disease reaching the end stage; history of allergic reactions to FPV or LPV/RTV; pregnant and lactating women; women after miscarriage or two weeks after delivery; patients participating in another clinical trial during the study or in the last 28 days prior to the study.</li></ul> |   |  |  |                                      |              |                    |
| Study limitations: risk of selection error. Still, the characteristics of patients included in the individual study arms were similar   | Median time until virus elimination**; number of days (IQR)   | Up to 14 days or until virus elimination  | 4 (2.5-9)  | 11 (8-13)  | P<0.001 SS^                          | N/A          |                    |
|   | Changes in the result of computed lung tomography^^ (improvement)   | after 14 days of treatment  | 32/35.   | 28/45.   | RR=1.47 (1.15; 1.89)<br>p=0.002      | 4 (3; 9)*    |                    |
|   | Adverse effects: total  | After 14 days of therapy  | 4/35, 11.43%   | 25/45, 55.56%  | OR=0.21 (0.08; 0.54),<br>p=0.001     | N/A          |                    |
|   | No statistically significant differences in the following adverse events: changes in the result of lung CT after 4 days of treatment (improvement, deterioration, no changes), changes in the result of lung CT after 14 days of treatment (deterioration, no changes), diarrhoea, nausea, rash, kidney and liver damage, other adverse effects   |   |  |  |                                      |              |                    |
| <b>Conclusions: A historically controlled experimental trial on the use of favipiravir in mild COVID-19 (patients previously treated with lopinavir and ritonavir and small patient groups) demonstrated a statistically significant and clinically relevant advantage of favipiravir over lopinavir used in combination with ritonavir in terms of virus elimination, improved radiological image of the lungs, as well as lower frequency of adverse effects. Surrogate endpoints. Low reliability study.</b> |   |   |  |  |                                      |              |                    |

\*own calculations of the Agency's analysts; <sup>^</sup>data derived directly from the study; <sup>^^</sup>a non-parametric Mann-Whitney U test was performed in the study to assess the statistical significance of differences in the changes in the result of computed lung tomography. As a result, on days 4 and 9, no statistically significant differences were found (the p-value amounted to 0.43 and 0.11, respectively), while 14 days after the first dose, a statistically significant difference in favour of favipiravir was found (p=0.004); \*\* virus elimination was concluded in the study when two negative qPCR test results were obtained 24 hours apart; N/A – not applicable; NDA – no data available

### 2.1.1.7. Lopinavir/ritonavir

| <b>Recommendation</b>  |
|--|
| In the absence of confirmed efficacy data, routine use of lopinavir/ritonavir is not recommended; its use should be restricted to clinical trials. |

**Justification:**

Five studies on lopinavir/ritonavir in COVID-19 have been identified: Deng 2020, which compared lopinavir/ritonavir to the combination of lopinavir/ritonavir + arbidol, Zhu 2020 comparing lopinavir/ritonavir with arbidol monotherapy, two single arm studies, Qui 2020 and Yuan 2020, as well as Liu 2020, which compared the effects of the therapy between younger and older patients ( $\geq 60$  vs  $< 60$  years of age) – see the table below. 3 case series studies were also included, with the number of patients equal to or greater than 10: Liu 2020, Wan 2020 and Young 2020 – description available in the annex (Annex no. 3).

**Precautions:**

The drug should only be used in consultation with a clinical pharmacologist. The liquid form is reserved for patients who, for various reasons, cannot receive the drug orally. The drug should be administered with food for optimal absorption. The liquid form should be administered only through PVC or silicone feeding tubes (e.g. a large-diameter oropharyngeal tube or nasopharyngeal tube). Alcoholic ingredients are incompatible with polyurethane-based tubes.

Crushing the tablets is not recommended (it reduces exposure by approx. 50%), but may be considered if no other options are available. Possible drug interactions should be taken into account before administration. The main adverse effect is gastrointestinal intolerance. Liver function test results should be monitored during therapy.

**Table 40. Description of the methodology and study results regarding the efficacy and safety of lopinavir/ritonavir in COVID-19**

| Study methodology  | Population / endpoint  | Observation time   | Intervention  | Control  | Relative parameter (95% CI, p value),                                       | NNT/NNH (95% CI) | Clinical relevance |
|--|--|--|---|--|---|------------------|--------------------|
| <b>Deng 2020<sup>181</sup></b>   |  |  |   |  |   |                  |                    |
| <ul style="list-style-type: none"> <li>Retrospective, cohort, two-arm, single-centre observational study (<i>The Fifth Affiliated Hospital of Sun Yat-Sen University, China</i>)</li> <li>Duration of the study: from 17 January to 13 February 2020</li> </ul>  | <p>N = 16 vs 17;<br/>Average age (years): 41.8 vs 47.25;<br/>Men (%): 43.8 vs 58.8</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>diagnosed, laboratory-confirmed COVID-19;</li> <li>≥18 years of age;</li> <li>pneumonia not requiring invasive or non-invasive ventilation</li> </ul> |  | n=16<br>Arbidol + lopinavir/ritonavir (LPV/r)<br>Arbidol: 200 mg every 8h, p.o.;<br>lopinavir 400 mg/ritonavir 100 mg every 12h, p.o. | n=17<br>lopinavir/ritonavir (LPV/r)<br>lopinavir 400 mg/ritonavir 100 mg every 12h, p.o. | Current clinical practice<br><No established COVID-19 procedure in Poland.> |                  |                    |
| <p>Study limitation:</p> <ul style="list-style-type: none"> <li>the study arms differed in the percentage of patients receiving corticosteroids (6% vs 41%, p &lt;0.05);</li> <li>no endpoint defined; improvement/progression of pneumonia determined by CT;</li> <li>no results for day 14 of observation for this endpoint;</li> <li>the safety results were presented jointly for both study arms and without indicating the observation period;</li> <li>the publication did not state whether the number of patients tested positive for SARS-Cov-2 through a stool sample test was determined in the entire population or only among patients with improved pneumonia (chest CT)</li> </ul> | Negative SARS-Cov-2 test – nasopharyngeal swab   | Treatment duration: 5-21 days; assessment of endpoints on day 7 and day 14 | Day 7: 12/16 (75%);<br>Day 14: 15/16 (94%)  | Day 7: 6/17 (35%);<br>Day 14: 9/17 (53%)   | p=0.05  | -                | -                  |
|  | Progression or improvement of pneumonia determined via chest CT  |  | Improvement<br>Day 7: 11/16 (69%);<br>Day 14: NDA   | Improvement<br>Day 7: 5/17 (29%);<br>Day 14: NDA   | p=0.05  | -                | -                  |
|  | Positive SARS-Cov-2 test – stool sample  |  | Day 7: 3 / NDA  | Day 7: 1 / NDA   | p>0.05  | -                | -                  |
|  | Elevated bilirubin level   | Treatment duration: 5-21 days; endpoint assessment: NDA                    | 68.7%   |  | -   | -                | -                  |
|  | Gastrointestinal disorders (such as diarrhoea, nausea)   |  | 43.7%   |  | -   | -                | -                  |
|  | Discontinuation of treatment due to adverse events   |  | 0%  |  | -   | -                | -                  |

| Study methodology  | Population / endpoint  | Observation time   | Intervention   | Control                           | Relative parameter (95% CI, p value),                                       | NNT/NNH (95% CI)                           | Clinical relevance |
|--|--|--|--|-----------------------------------|---|--|--------------------|
| Zhu 2020 <sup>182</sup>  |  |  |  |                                   |   |  |                    |
| <ul style="list-style-type: none"><li>Two-centre retrospective study (Third People's Hospital in Changzhou and Second People's Hospital in Wuhan)</li><li>Duration of the study: from 23 January to 29 February 2020</li></ul> | Median age:<br>Lopinavir/ritonavir – 40.5 years (IQR 34.8-52.3)<br>Arbidol – 26.5 years (IQR 23.3-52.5)<br>Men:<br>Lopinavir/ritonavir - 20 (58.8%)<br>Arbidol - 6 (37.5%) |  | n=34<br>Lopinavir/ritonavir – 400 mg / 100 mg, 2 per day   | n=16<br>Arbidol – 0.2g, 3 per day | Current clinical practice<br><No established COVID-19 procedure in Poland>  |  |                    |
|  | Patients with COVID-19   |  |  |                                   |   |  |                    |
| Study limitation: <ul style="list-style-type: none"><li>small sample size</li></ul>  | Efficacy:<br>Viral load  | 14 days  | 15/34.   | 0/16.                             | RR=15.06 (95% CI: 0.96; 236.93), p=0.054)*                                  | NNH=3 (95%CI: 1.3; 3.6) <sup>#</sup>       | -                  |
|  | Safety:<br>Elevated ALT levels in week 1 of hospitalisation. (3 patients in the lopinavir/ritonavir arm and 3 patients in the arbidol arm)                                 |  | 3/34.  | 3/16.                             | RR=0.47 (95%CI: 0.11; 2.08), p=0.32)*                                       | NNT=11 (95%CI: (11.44; 31.30) <sup>#</sup> | -                  |
| Qiu 2020 <sup>183</sup>  |  |  |  |                                   |   |  |                    |
| <ul style="list-style-type: none"><li>Retrospective observational study, 3 hospitals in the Zhejiang Province</li><li>Study duration: from 17 January 2020 to 01 March 2020</li></ul>  | N=36<br>women – 13 (36%)<br>men – 23 (64%)<br>average age (SD; range) – 8.3 years (3.5, 1–16)  |  | n=36<br>IFN- $\alpha$ , aerosol, 2 times per day, (100%)<br>n=14<br>lopinavir–ritonavir, syrup, 2 times per day, (39%)<br>n=6<br>oxygen therapy, (17%) | Uncontrolled                      | Current clinical practice<br><No established COVID-19 procedure in Poland.> |  |                    |
|  | Paediatric patients aged 0-16 with laboratory-confirmed COVID-19   |  |  |                                   |   |  |                    |
| Study limitations: <ul style="list-style-type: none"><li>small sample size</li><li>early results</li></ul>   | Time until obtaining a negative result in the PCR test for SARS-CoV-2 for the  | The average length of hospitalisation – 14 days. Data on lop/rit treatment | 10 (2.7-22)<br>On 28/02/2020, all patients were considered cured   | -                                 | -   | -  | -                  |

| Study methodology   | Population / endpoint   | Observation time  | Intervention                                  | Control      | Relative parameter (95% CI, p value),                                   | NNT/NNH (95% CI) | Clinical relevance |
|---|---|---|---|--------------|---|------------------|--------------------|
| <ul style="list-style-type: none"><li>no safety assessment was performed</li></ul>  | General population, days (SD, range)  | time was given for 3 patients; it was on average 5-6 days |   |              |   |                  |                    |
|   | Duration of hospitalisation for the general population, days (SD, range)      |   | 14 (3, 10-20)                                 | -            | -   | -                | -                  |
|   | Fever duration after admission for the general population, days (SD, range)   |   | 3 (2, 2-5)                                    | -            | -   | -                | -                  |
| Yuan 2020 <sup>184</sup>  |   |   |   |              |   |                  |                    |
| <ul style="list-style-type: none"><li>Single-centre retrospective study (Shenzhen Third People's Hospital)</li><li>Data on patients admitted between 11 January 2020 and 4 February 2020.</li></ul>   | N = 94<br>mild form, n = 8, moderate form, n = 75, acute form, n = 11         |   | IFN-α + lopinavir/ritonavir, n=46             | Uncontrolled | Current clinical practice <No established COVID-19 procedure in Poland> |                  |                    |
|   | Average age 40 years (range: 1.-78.<br>Men 42 (45%)<br>Women 52 (55%)         |   | IFN-α + lopinavir/ritonavir + ribavirin, n=21 |              |   |                  |                    |
|   | Patients with COVID-19  |   |   |              |   |                  |                    |
| Study limitation: <ul style="list-style-type: none"><li>only 94 discharged patients were included</li><li>only a qualitative analysis of viral mRNA was performed (further quantitative analysis of COVID-19 could be more useful to accurately assess the efficacy of various therapeutic regimens)</li><li>no safety assessment was performed</li></ul> | Average duration of hospitalisation for the general population, days (95% CI) | Average treatment duration – 14.11 days (given for IFN-α) | 14.28 (13.61-14.95);                          | -            | -   | -                | -                  |
|   | PCR negative conversion rate in hospitalised patients                         |   | Day 0 – 41.07%<br>Day 15 – 95.45%             | -            | -   | -                | -                  |

| Study methodology  | Population / endpoint   | Observation time                           | Intervention  | Control   | Relative parameter (95% CI, p value),                                    | NNT/NNH (95% CI) | Clinical relevance |
|--|---|--|---|---|--|------------------|--------------------|
| Liu 2020 <sup>185</sup>  |   |  |   |   |  |                  |                    |
| <ul style="list-style-type: none"> <li>Two-arm retrospective observational study (comparison of two age groups)</li> <li>Single-centre (Hainan Provincial People's Hospital, China)</li> <li>Duration of the study: from 15 January to 18 February 2020</li> </ul>   | <p>N=56;<br/>Patients ≥60 years of age, n=18 (median age – 68, men – 66.7%)<br/>vs patients ≥60 years of age, n=38 (median age – 47, men – 50%)</p> <p>Patients with confirmed pneumococcal pneumonia in COVID-19</p> |  | <p>Patients ≥60 years old;<br/>lopinavir/ritonavir p.o. 16/18 (83.33%);<br/>in addition:<br/>interferon inhalations, non-antiviral treatment, traditional Chinese medicine, antibiotics, immunoglobulins, thymopentin, continuous renal replacement therapy; oxygen therapy<br/>Dosage: NDA</p> | <p>Patients &lt; 60 years old;<br/>lopinavir/ritonavir p.o. 37/38 (86.84%);<br/>in addition:<br/>interferon inhalations, non-antiviral treatment, traditional Chinese medicine, antibiotics, immunoglobulins, thymopentin, continuous renal replacement therapy; oxygen therapy<br/>Dosage: NDA</p> | Current clinical practice <No established COVID-19 procedure in Poland.> |                  |                    |
| <p>Study limitations:</p> <ul style="list-style-type: none"> <li>the study compared different age groups, not therapies;</li> <li>not all patients were receiving lopinavir/ritonavir;</li> <li>no information on drug dosage;</li> <li>no information on treatment time/observation period;</li> <li>for some of the endpoints no figures were given, only information about the direction of differences between the arms</li> </ul> | Involvement of multiple lung lobes – chest CT result (% of patients)  | Treatment duration/observation period: NDA | 16/18 (88.89%)  | 24/38 (63.16%)  | (n/e)<br>p=0.001   | n/e              | -                  |
|  | Involvement of a single lung lobe (% of patients)   |  | 2/18 (11.11%)   | 14/38 (36.84%)  | (n/e)<br>p=0.824   | n/e              | -                  |
|  | PSI indicator   |  | higher in the ≥60 years of age arm:   |   | (n/e)<br>p=0.001   | n/e              | -                  |
|  | Patient percentage: with PSI IV or V  |  | higher in the ≥60 years of age arm:   |   | (n/e)<br>p=0.05  | n/e              | -                  |
|  | Cured patients (%)  |  | 17/18 (94.44%)  | 36/38 (94.74%)  | n/e  | n/e              | -                  |
|  | Deaths  |  | 1/18 (5.56%)  | 2/38 (5.26%)  | n/e  | n/e              | -                  |

NDA – no data available; CT – computed tomography; n/e – not evaluated (the analysts abandoned estimating relative parameters, as the study did not compare lopinavir/ritonavir therapy with other therapies or the lack thereof – only two age groups of patients were compared); PSI – Pneumonia Severity Index (range between I and V, the higher the value, the worse the patient's condition)

\*analysts' own calculations (ZawEkk\_v1.5; Mantel-Haenszel method, Fixed effect); # analysts' own calculations

#### 2.1.1.8. Azithromycin

| <b><i>Recommendation</i></b>  |
|---|
| In the absence of confirmed efficacy data, routine use of azithromycin is not recommended; its use should be restricted to clinical trials. |

No studies assessing the efficacy and safety of azithromycin monotherapy in COVID-19 were identified in the course of the review. The only identified studies relating to the use of azithromycin in COVID-19 are: Gautret 2020b<sup>186</sup>, an observational study assessing hydroxychloroquine with azithromycin and a non-randomised controlled clinical trial, in which, azithromycin was added as a prophylaxis for bacterial superinfection in some patients treated with hydroxychloroquine (Gautret 2020a<sup>187</sup>) and a series of 11 case studies – Molina 2020<sup>188</sup>, in which hydroxychloroquine therapy was used in combination with azithromycin according to the dosing regimen used in Gautret 2020a – (Gautret 2020a<sup>189</sup>) – table below.

**Table 41. Description of the methodology and results of Gautret 2020a and Molina 2020 – azithromycin**

| Methodology  | Population / endpoint   | Observation time | Intervention  | Control   | Relative parameter (95% CI)  | NNT (95% CI)        | Clinical relevance |                                 |                     |                                  |                    |   |
|--|---|------------------|---|---|--|---------------------|--------------------|---------------------------------|---------------------|----------------------------------|--------------------|---|
| Gautret 2020a <sup>164</sup>   |   |                  |   |   |  |                     |                    |                                 |                     |                                  |                    |   |
| Controlled clinical trial with a control group from a different centre (study group in Marseilles, data for the control group derived from other centres in France);<br>Study from early March 2020 to 16 March 2020   | ITT: N=42, including:<br>N1 = 26 vs N2 = 16<br>Per protocol: N=36<br>n1 = 20 vs n2 = 16<br>Average age: 45.1 (SD: 22.0), HCQ: 51.2 vs control: 37.3<br>Men: 41.7 %; vs 37.5%.<br>Asymptomatic: 16.7%; vs 25%.<br>Average time from the onset of symptoms: 4.0 days  | 14 days          | n=26<br>6 patients were lost: 3 was moved to ICU; 1 died on day 3. (PCR-negative); 1 was discharged; 1 discontinued treatment<br>Hydroxychloroquine 200 mg, 3 per day for 10 days (N=20).<br>+ symptomatic treatment and antibiotics (prophylaxis of bacterial superinfection.<br><b>(Azithromycin was used in 6/20 patients)</b> | n=16 symptomatic treatment<br>no data on the treatment used | Current clinical practice: in Poland – no established COVID-19 procedure                       |                     |                    |                                 |                     |                                  |                    |   |
| Limitations:<br>no randomisation; loss of 6 patients from the study arm; the trial protocol did not include a control arm, the control arm comprised of patients from a different centre and those who did not agree to participate in the study; small sample size; small size; age difference between the arms; no data on treatment in the control arm; the assessment time was modified in relation to the protocol and the results for days 7 and 14 after inclusion and after discharge were not presented, <b>Journal Pre-Proof</b>   | Hospitalised patients with SARS-CoV-2 documented in PCR in nasopharyngeal samples, >12 years old.<br>Patients with CQ or HCQ allergy and retinopathy, G6PD deficiency and QT prolongation were excluded.  |                  |   |   | Negative PCR in nasopharyngeal samples ( <b>post hoc analysis for the HCQ + AZY subgroup</b> ) |                     | Day 3              | HCQ+AZY: 5/6(83.3%)             | 1/16 (6.3%)         | RR = 13.33 (95% CI: 1.93; 91.97) | NNT = 2 (0.9; 2.2) | - |
|  |   |                  |   |   | Day 4  | HCQ+AZY:5/6 (83.3%) | 4/16 (25%)         | RR = 3.33 (95% CI: 1.33; 8.37)  | NNT = 2 (1.1; 4.6)  | -                                |                    |   |
|  |   |                  |   |   | Day 5  | HCQ+AZY: 6/6 (100%) | 3/16 (18.8%)       | RR = 5.33 (95% CI: 1.92; 14.79) | NNT = 2 (1.0; 1.6)  | -                                |                    |   |
|  |   |                  |   |   | Day 6  | HCQ+AZY: 6/6 (100%) | 2/16 (12.5%)       | RR = 8 (95% CI: 2.19; 29.25)    | NNT = 3 (1.4; 20.4) | -                                |                    |   |
|  | It is noteworthy that one patient who was still PCR-positive on day 6 after hydroxychloroquine treatment, received additional azithromycin on day 8 and her PCR was negative on day 9. In contrast, one of the patients treated with hydroxychloroquine and azithromycin, who obtained a negative result on day 6, tested positive (low load) on day 8. |                  |   |   |  |                     |                    |                                 |                     |                                  |                    |   |
| <b>Conclusions: Very low reliability of the trial – small sample, very uncertain possibility of comparing the results of the experimental arm and the control arm, made up partly of patients from other centres. Initially, both arms were characterised by significant differences, as clearly seen in the age – in this case, the fact that the average age of the experimental arm was greater seems to favour positive results (Covid-19 has a worse prognosis in older patients). In addition, the result is distorted due to a large observation loss (6 out of 26) and the fact that azithromycin is used in only one arm (in 6 out of 20) and, as suggested by subgroup analyses, this drug impacted the results.</b> |   |                  |   |   |  |                     |                    |                                 |                     |                                  |                    |   |

| Methodology   | Population / endpoint   | Observation time | Intervention   | Control | Relative parameter (95% CI) | NNT (95% CI) | Clinical relevance   |
|---|---|------------------|--|---------|-----------------------------|--------------|--|
| <b>Gautret 2020b<sup>165</sup></b>  |   |                  |  |         |                             |              |  |
| Single-centre observational study<br>Duration of the study: from 03/03/2020 to 21/03/2020 (patient inclusion)     | N=80<br>Median age: 52 years (18-88); Men: 53.8%;<br>Average time since symptom onset: 4.8 days (range: 1-17 days); Fever: 15% of patients);<br>Asymptomatic patients: 5%;<br>57.5% of patients had ≥1 known risk factor (hypertension, diabetes or chronic respiratory disease);   | At least 6 days  | Hydroxychloroquine 200 mg, 3 per day + azithromycin (500 mg on D1, then 250 mg per day for the next 4 days).<br>In patients with pneumonia and the NEWS (The national early warning score) ≥5, ceftriaxone was added to HCQ and azithromycin (used in 8%).<br>93.7% of patients received the first dose of drugs within 1 day from admission.<br>79/80 patients were treated on a daily basis throughout the study period, which lasted up to 10 days (1 patient discontinued treatment on day 4 due to potential interactions with other drugs) |         |                             |              | Current clinical practice: in Poland – no established COVID-19 procedure |
|   | Study population (inclusion criteria): Hospitalised patients with SARS-CoV-2 documented in PCR in nasopharyngeal samples.<br>The analysis included all patients who were treated with hydroxychloroquine and azithromycin for at least three days and who were under observation for at least six days (the study included 6 patients using hydroxychloroquine with azithromycin from Gautret 2020a). |                  |  |         |                             |              |  |
| Study limitations: no control arm; no accurate information on the observation period;<br><b>Journal Pre-Proof</b> | Oxygen therapy  | At least 6 days  | n=12 (15%)   |         | N/A                         | N/A          | -  |
|   | Transfer to ICU   | At least 6 days  | n=3 (3.8%)   |         | N/A                         | N/A          | -  |
|   | Death   | At least 6 days  | n=1 (1.2%)   |         | N/A                         | N/A          | -  |
|   | Discharge   | At least 6 days  | n=65 (81.2%)   |         | N/A                         | N/A          | -  |
|   | Hospitalisation during data collection  | At least 6 days  | Intensive care: n=1 (1.2%)<br>Isolation ward: n=13 (16.2%)   |         | N/A                         | N/A          | -  |
|   | Administration of other antibiotics   | At least 6 days  | n=18 (22.5%)   |         | N/A                         | N/A          | -  |
|   | Time from start of treatment to discharge (for 65 discharged patients)  | At least 6 days  | Average: 4.1 days (SD: 2.2) Range: 1-10 days   |         | N/A                         | N/A          | -  |
|   | Length of stay in the isolation ward (for 65 discharged patients)   | At least 6 days  | Average: 4.6 days (SD: 2.1) Range: 1-11 days   |         | N/A                         | N/A          | -  |

| Methodology  | Population / endpoint   | Observation time    | Intervention   | Control | Relative parameter (95% CI)                  | NNT (95% CI) | Clinical relevance |
|--|---|---------------------|--|---------|--|--------------|--------------------|
|  | Negative qPCR in nasopharyngeal samples   | On day 7            | n=no data (83%)  |         | N/A  | N/A          | -                  |
|  |   | On day 8            | n=no data (93%)  |         | N/A  | N/A          | -                  |
|  | Nausea or vomiting  | At least 6 days     | n=2 (2.5%)   |         | N/A  | N/A          | -                  |
|  | Diarrhoea   | At least 6 days     | n=4 (5.0%)   |         | N/A  | N/A          | -                  |
|  | Blurred image after 5 days of treatment   | 5 days of treatment | n=1 (1.2%)   |         | N/A  | N/A          | -                  |
| Molina 2020 <sup>190</sup>   |   |                     |  |         |  |              |                    |
| Case series description (Infectious Diseases Department, AP-HP-Saint-Louis Hospital, France). Observation period: 6 days | N=11<br>Median age: 58.7 (range: 20-77);<br>Percentage of men: 63.6%; Percentage of women: 36.4%;<br>8/11 patients with significant comorbidities associated with worse results (obesity: 2; solid tumours: 3; haematological cancers: 2; HIV infection: 1); 10/11 experienced fever at the start of treatment and received nasal oxygen therapy. |                     | <b>Hydroxychloroquine</b> 600mg/day (200 mg, 3 per day) for 10 days<br><b>+Azithromycin (500 mg on D1, then 250 mg per day for the next 4 days).</b> | N/A     | No established COVID-19 procedure in Poland. |              |                    |
| Hospitalised patients with SARS-CoV-2 documented in PCR in nasopharyngeal samples.                                       |   |                     |  |         |  |              |                    |
| Study limitations:<br>- no randomisation,<br>- no control arm.   | Positive PCR test for SARS-CoV2 RNA   | Days 5-6            | n=8/10** (80%, 95% CI: 49–94)<br>** not performed in the deceased patient  | N/A     | N/A  | N/A          | -                  |
|  | Death   | 5 days              | n=1/11 (9%)  | N/A     | N/A  | N/A          | -                  |
|  | Transfer to ICU   | 5 days              | n=2/11 (18%)   | N/A     | N/A  | N/A          | -                  |
|  | QT prolongation requiring discontinuation of therapy  | 5 days              | n=1/11 (9%)  | N/A     | N/A  | N/A          | -                  |

### 2.1.1.9. Corticosteroids

| <b>Recommendation</b>  |
|--|
| Routine use of systemic corticosteroids in mechanically ventilated adult COVID-19 patients with respiratory failure WITHOUT acute respiratory distress syndrome – ARDS is discouraged.   |
| In adult patients with COVID-19 and refractory septic shock, the use of low-dose corticosteroids is recommended. Typical daily corticosteroid dosing in patients with septic shock is 200 mg of hydrocortisone administered by intravenous infusion or intermittent doses. |
| In mechanically ventilated COVID-19 patients with acute respiratory distress syndrome (ARDS), using systemic corticosteroids are suggested.  |

#### **Justification:**

Numerous observational studies have been published regarding the use of corticosteroids in the treatment of viral pneumonia (e.g. influenza virus, coronavirus and others). However, drawing conclusions on their basis is uncertain, as usually patients with more severe disease progression are treated using corticosteroids. The Cochrane review update on the use of corticosteroids in the treatment of influenza<sup>191</sup> included 15 cohort studies for influenza and 10 for coronaviruses. The adjusted odds ratio (OR) indicates a relationship between the use of corticosteroids and an increased risk of death [OR = 2.76; (95% CI: 2.06-3.69)]. Nonetheless, the results of analyses in the group of coronavirus patients indicate no statistically significant differences in the analysed endpoint [OR = 0.83; (95% CI: 0.32–2.17)]. The high heterogeneity of the included studies should also be kept in mind.

Both the 2018 systematic review of 22 RCTs (n = 7297 patients), comparing low-dose corticosteroid therapy with the lack thereof in adult patients in septic shock<sup>192</sup>, as well as the clinical guidelines<sup>193</sup>, reported no statistically significant differences in short-term mortality [RR = 0.96; (95% CI: 0.91-1.02)], long-term mortality [RR = 0.96; (95% CI 0.90-1.02)] or the number of serious adverse events (RR = 0.98; (95% CI: 0.90-1.08)).

There are no controlled clinical trials on the use of corticosteroids in patients with COVID-19 or infected with other coronaviruses. A published, nonreviewed report on 26 patients with severe COVID-19 indicates that the use of methylprednisolone at a dose of 1-2 mg/kg/day for 5-7 days was associated with a shorter period of oxygen supplementation (8.2 days vs 13.5 days; p < 0.001) and improved radiographic results.<sup>194</sup> Notwithstanding, the authors of the guidelines assessed that due to the risk of error, these preliminary reports do not constitute a sufficient basis for formulating recommendations. Therefore, the recommendations were based on indirect evidence regarding community-acquired pneumonia, acute respiratory distress syndrome and other viral infections.

There are several randomised trials on the use of systemic corticosteroids in hospitalised patients (usually not as part of intensive care), patients with community-acquired pneumonia, as well as some patients with sepsis or septic shock. A systematic review and meta-analysis of RCTs demonstrated that the use of corticosteroids may result in reduced necessity of mechanical ventilation (5 RCT; 1,060 patients; RR = 0.45, 95% CI: 0.26 – 0.79), reduced ARDS (4 RCT; 945 patients; RR = 0.24, 95% CI: 0.10 – 0.56) and reduced hospitalisation time (6 RCT; 1,499 patients; MD = 1.00 days, 95% CI: -1, 79 to -0.21), but increases the risk of treatment-requiring hyperglycaemia.<sup>195</sup> These trials included different populations, different drugs and dosages were used, and the impact of treatment on mortality was inconclusive. There are also some concerns regarding the use of corticosteroids in viral pneumonia. Therefore, it is not possible to clearly relate these results to the COVID-19 population.

## Fluid therapy

| <b><i>Recommendation</i></b>   |
|--|
| In the event of acute resuscitation of adult COVID-19 patients in shock, adopting a conservative approach to fluid therapy instead of a liberal approach is suggested. |

### ***Justification:***

Due to the lack of evidence for COVID-19 patients in shock, it was decided to indirectly use evidence for patients in critical condition with sepsis and ARDS to formulate this recommendation.

The most recent systematic review, which included a meta-analysis of 9 RCTs (n=637 patients) comparing the conservative and liberal approach to fluid volume used in the initial resuscitation of patients with sepsis, showed no statistically significant difference in mortality (RR = 0.87, 95% CI 0.69–1.10) or the occurrence of serious adverse events (RR = 0.91, 95% CI 0.78–1.05) between the examined arms<sup>196</sup>. However, all the assessed endpoints favour the conservative approach (smaller fluid volumes). The quality of evidence was assessed as very low, at the same time highlighting the need for more research in this area.

**Safety precautions:** crystalloids should be preferred over colloidal agents in fluid therapy.

## 2.1.2. Procedure depending on the severity of COVID-19

### Authors' remark

The opinions formulated by the panel are based on the analysis of the current available guidelines for therapeutic procedure in COVID-19. The analysis of scientific evidence from clinical trials, previously presented for each of the discussed drug technologies, was prepared in parallel with the work of the panel of experts. At the time of formulating their opinion, the panel did not know the results of this analysis and relied mainly on the existing guidelines.

**Taking into account the results of the analysis of the available scientific reports (see: chapter 2.1.1), it should be emphasised that, currently, there is no evidence confirming the greater clinical benefit of using one of the available COVID-19 therapeutic options.**

Table 42. Summary – recommendations of selected drugs (rows) by individual guidelines (columns) in the treatment of COVID-19.

|                                | World | Europe       | Poland   | USA  |     |     |        | China   |        | Korea | Italy | Belgium | UK      | Spain | Australia | India    | Netherlan | Canada     |      | France |
|--------------------------------|-------|--------------|----------|------|-----|-----|--------|---------|--------|-------|-------|---------|---------|-------|-----------|----------|-----------|------------|------|--------|
|                                | WHO   | SCCM & ESICM | PTEILChZ | UPHS | MHS | MGH | ATSITF | NHC-PRC | CHZUSM | NUS   | NIID  | ITM     | The BMJ | SSHP  | NSW       | MH India | NIHEN     | Gov Canada | MCMH | FRS    |
| BASIC LIST                     |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| chloroquine                    |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| hydroxychloroquine             |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| lopinavir/ritonavir            |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| remdesivir                     |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| tocilizumab                    |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| favipiravir                    |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| oseltamivir                    |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| azithromycin                   |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| convalescent plasma            |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| ADDITIONAL LIST                |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| interferon $\alpha$ or $\beta$ |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| steroids                       |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| heparins                       |       |              |          |      |     |     |        |         |        |       |       |         |         |       |           |          |           |            |      |        |
| combined therapy*              |       |              | 1        | 2    | 3   | 4   |        | 5       |        | 6     | 7     |         |         |       | 8         | 9        |           |            |      |        |

\*All combination therapies referred to in the recommendations have been included

- 1) lopinavir/ritonavir + chloroquine or hydroxychloroquine, lopinavir/ritonavir + chloroquine or hydroxychloroquine + tocilizumab
- 2) lopinavir/ritonavir + ribavirin
- 3) lopinavir/ritonavir + amiodarone, quetiapine or simvastatin
- 4) hydroxychloroquine + remdesivir
- 5) ribavirin + interferon or lopinavir/ritonavir
- 6) lopinavir/ritonavir + chloroquine or hydroxychloroquine
- 7) chloroquine/hydroxychloroquine + lopinavir/ritonavir or darunavir + ritonavir, lopinavir/ritonavir + chloroquine or hydroxychloroquine + tocilizumab
- 8) lopinavir/ritonavir +/- hydroxychloroquine
- 9) hydroxychloroquine + azithromycin

WHO – World Health Organisation  
 SCCM & ESICM – Society of Critical Care Medicine and the European Society of Intensive Care Medicine  
 PTEiLChZ – Polish Society of Epidemiologists and Infectious Disease Doctors  
 UPHS – University of Pennsylvania Health System  
 MHS – Military Health System  
 MGH – Massachusetts General Hospital  
 ATSITF – American Thoracic Society-led International Task Force  
 NHC-PRC – National Health Commission, PRC  
 CHZUSM – Children's Hospital, Zhejiang University School of Medicine  
 NUS – NUS Saw Swee Hock School of Public Health  
 NIID – National Institute for the Infectious Diseases "L. Spallanzani", IRCCS  
 ITM – Institute of Tropical Medicine in Antwerp  
 BMJ – The British Medical Journal  
 SSHP – Spanish Society of Hospital Pharmacy  
 NSW – New South Wales Government, Department of Health  
 MH India – Government of India, Ministry of Health & Family Welfare Directorate General of Health Services  
 NIHEN – The National Institute for Health and the Environment of the Netherlands  
 Gov Canada - Government of Canada  
 MCMH – British Columbia Ministry of Health  
 FRS – French Resuscitation Society

|  |                                      |
|--|--------------------------------------|
|  | not recommended                      |
|  | no reference                         |
|  | optional in co-infection (influenza) |
|  | optional or can be considered        |
|  | recommended                          |

### 2.1.2.1. Asymptomatic patients or patients with mild symptoms

| <b>Recommendation</b>                   |
|---|
| 2.1.2.1.1. Treatment: symptomatic only. |

### 2.1.2.2. Symptomatic patients without signs of respiratory failure

| <b>Steering Committee Recommendation</b>  |
|---|
| 2.1.2.2.1. In the absence of scientific evidence confirming the efficacy of lopinavir/ritonavir +/- chloroquine or hydroxychloroquine, routine use of lopinavir/ritonavir +/- chloroquine or hydroxychloroquine is not recommended; their use should be restricted to clinical trials.  |
| <b>Expert Panel Opinion</b>   |
| <p>Due to insufficient data resulting from the lack of complete clinical data usually required when applying for marketing authorisation in a particular indication, decisions about basic treatment should be made individually by the practitioner.</p> <p>Based on incomplete knowledge and availability of drugs in therapy, the following may be considered in selected patients:</p> <ul style="list-style-type: none"> <li>• Lopinavir/ritonavir, administered orally (do not crush) 400/100 mg every 12 hours, 14 days +</li> <li>• Chloroquine, administered orally (crushing is acceptable), for 3 days: 500 mg every 12 hours, and then for 4-7 days, 250 mg every 12 hours (no longer than 10 days) or Hydroxychloroquine,</li> </ul> |

|   |
|---|
| orally (crushing is acceptable), loading dose: 400 mg every 12 hours, maintenance dose: 200 mg every 12 hours, 10 days. |
|---|

**Note:**

The use of the following combination therapies: lopinavir/ritonavir +/- chloroquine or hydroxychloroquine (+ tocilizumab in patients in more severe condition) is recommended in the Italian NIID guidelines or in the guidelines of the Polish Society of Epidemiologists and Infectious Disease Doctors, based thereon. In line with the Australian NSW guidelines, the combination of lopinavir/ritonavir with hydroxychloroquine may be considered in individual cases.

The Korean guidelines (NUS) emphasise the lack of evidence proving that the use of lopinavir/ritonavir with chloroquine or hydroxychloroquine is more efficacious than monotherapy. Combining these drugs can cause serious arrhythmias due to the prolongation of the QT interval. Therefore, extreme caution should be exercised when these drugs are co-administered. The Dutch (The National Institute for Health and the Environment of the Netherlands, NIHE), French (French Resuscitation Society, FRS) and Belgian (Institute of Tropical Medicine in Antwerp, ITM) guidelines also suggest monotherapy.

**It should be emphasised that, currently, there are no available clinical data allowing to conclude on the superiority of the combination therapy consisting of lopinavir/ritonavir + chloroquine or hydroxychloroquine over chloroquine or hydroxychloroquine used as monotherapy.**

### 2.1.2.3. Patients in severe condition with respiratory failure (pre-ARDS)

| <b>Steering Committee Recommendation</b>   |
|--|
| 2.1.2.3.1. In the absence of scientific evidence confirming the efficacy of lopinavir/ritonavir +/- chloroquine or hydroxychloroquine or tocilizumab, routine use of the above-mentioned therapy is not recommended; their use should be restricted to clinical trials.  |
| <b>Expert Panel Opinion</b>  |
| <p>Due to insufficient data resulting from the lack of complete clinical data usually required when registering a drug for use in a particular indication, decisions about basic treatment should be made individually by the practitioner.</p> <p>Based on incomplete knowledge and availability of drugs, the following therapy regimen may be considered:</p> <ul style="list-style-type: none"> <li>• Lopinavir/ritonavir, administered orally (do not crush) 400/100 mg every 12 hours, 28 days<br/>+</li> <li>• Chloroquine, administered orally (crushing is acceptable), for 3 days: 500 mg every 12 hours, and then for 4-7 days, 250 mg every 12 hours (no longer than 10 days) or Hydroxychloroquine, orally (crushing is acceptable), loading dose: 400 mg every 12 hours, maintenance dose: 200 mg every 12 hours, 10 days<br/>+</li> <li>• Tocilizumab (in patients with elevated IL-6), administered intravenously 8 mg/kg (maximum 800 mg) as a single dose (one-hour infusion), in the absence of improvement, the second dose may be repeated after 8-12 hours.</li> </ul> |

**Note:**

It should be emphasised that, currently, there are no available clinical data allowing to conclude on the superiority of the combination therapy consisting of lopinavir/ritonavir + chloroquine or hydroxychloroquine over chloroquine or hydroxychloroquine used as monotherapy.

In the event of a significant increase in IL-6 concentration, inhibiting the cytokine storm has a pathophysiological justification. Tocilizumab blocks the IL-6 receptor; however, its efficacy and safety has not been sufficiently confirmed yet. (see 0) Therefore, only administering this drug as part of a clinical trial can be considered.

**Steering Committee Recommendation**

2.1.2.3.2. Routine use of low-molecular-weight heparins in prophylactic doses in severe COVID-19 patients is recommended due to the risk of deep vein thrombosis and pulmonary embolism. In the event of thrombosis, pulmonary embolism, disseminated intravascular coagulation or catastrophic antiphospholipid syndrome – in therapeutic doses.

**Expert Panel Opinion**

The use of low-molecular-weight heparins constitutes adjunctive therapy.

**Steering Committee Recommendation**

2.1.2.3.3. Routine use of systemic corticosteroids in mechanically ventilated adult COVID-19 patients with respiratory failure WITHOUT acute respiratory distress syndrome – ARDS is discouraged.

**Expert Panel Opinion**

Glucocorticoids may be used in exceptional cases, especially in the absence of improvement after tocilizumab treatment.

#### 2.1.2.4. Patients in critical condition with ARDS

| <b>Steering Committee Recommendation</b>   |
|--|
| 2.1.2.4.1. In the absence of scientific evidence confirming the efficacy of lopinavir/ritonavir +/- chloroquine or hydroxychloroquine or tocilizumab, routine use of the above-mentioned therapy is not recommended; their use should be restricted to clinical trials.  |
| <b>Expert Panel Opinion</b>  |
| <p>Due to insufficient data resulting from the lack of complete clinical data usually required when registering a drug for use in a particular indication, decisions about basic treatment should be made individually by the practitioner.</p> <p>Based on incomplete knowledge and availability of drugs, the following therapy regimen may be considered:</p> <ul style="list-style-type: none"><li>• Lopinavir/ritonavir, administered orally (do not crush) 400/100 mg every 12 hours, 28 days +</li><li>• Chloroquine, administered orally (crushing is acceptable), for 3 days: 500 mg every 12 hours, and then for 4-7 days, 250 mg every 12 hours (no longer than 10 days) or Hydroxychloroquine, orally (crushing is acceptable), loading dose: 400 mg every 12 hours, maintenance dose: 200 mg every 12 hours, 10 days +</li><li>• Tocilizumab, administered intravenously, 8 mg/kg (maximum 800 mg) as a single dose (one-hour infusion), in the absence of improvement, the second dose may be repeated after 8-12 hours.</li></ul> |
| <p><b>Note:</b></p> <p><b>It should be emphasised that, currently, there are no available clinical data allowing to conclude on the superiority of the combination therapy consisting of lopinavir/ritonavir + chloroquine or hydroxychloroquine over chloroquine or hydroxychloroquine as monotherapy. In the event of a large increase in IL-6 concentration, inhibiting excessive cytokine activity is pathophysiologically justified. Such an effect can be obtained with tocilizumab. However, due to the (current) lack of sufficient confirmation of its efficacy and safety (see 0), administration of the drug may be considered only as part of the clinical trial.</b></p>  |

| <b>Steering Committee Recommendation</b>   |
|--|
| 2.1.2.4.2. Routine use of low-molecular-weight heparins in prophylactic doses in severe COVID-19 patients with ARDS is recommended, due to the risk of deep vein thrombosis and pulmonary embolism. In the event of thrombosis, pulmonary embolism, disseminated intravascular coagulation or catastrophic antiphospholipid syndrome – in therapeutic doses. |
| <b>Expert Panel Opinion</b>  |
| The use of low-molecular-weight heparins constitutes adjunctive therapy.   |

**Steering Committee Recommendation**

2.1.2.4.3. In adult patients with COVID-19 and refractory septic shock, the use of low-dose corticosteroids is recommended. Typical daily corticosteroid dosing in patients with septic shock is 200 mg of hydrocortisone administered by intravenous infusion or intermittent doses.

2.1.2.4.4. In mechanically ventilated COVID-19 patients with acute respiratory distress syndrome (ARDS), using systemic corticosteroids is suggested.

**Expert Panel Opinion**

Glucocorticoids may be used in exceptional cases, especially in the absence of improvement after tocilizumab treatment.

**Expert Panel Opinion**

The following drugs have potential therapeutic value in COVID-19 but require further research:

1. Remdesivir
2. Convalescent plasma
3. Interferon alfa or beta

Contrary to some opinions, the following drugs are not efficacious in COVID-19 treatment:

1. Azithromycin – may be considered in COVID-19 in justified cases involving bacterial infection, in line with the principles of antibiotic therapy.

Oseltamivir – may be considered in COVID-19 in justified cases involving co-infection with the influenza virus.

## 2.2. Oxygen therapy

### Authors' remarks

*Dyspnoea (shortness of breath) is a relatively common symptom of COVID-19. It was found in 31.2% of the 138 patients hospitalised due to this disease in one of the Wuhan hospitals<sup>197</sup>. In other studies, the percentage of patients suffering from dyspnoea was even greater and ranged between 42 and 55%<sup>198,199</sup>. The course of the disease varies and is estimated to be severe or very severe in approx. 20% of patients. The most important factor determining the disease course are gas exchange abnormalities, in particular hypoxaemia.<sup>200</sup> Available studies indicate that approx. 70-80% of patients admitted to hospitals due to pneumonia caused by SARS CoV-2 require oxygen therapy.<sup>201</sup> Results of a different study which analysed 201 COVID-19-related pneumonia cases indicate the efficacy of passive oxygen therapy with the use of  $\text{FiO}_2 < 0.6$  in 72% patients<sup>202</sup>. The remaining 28% of patients had to be admitted to the Intensive Care Unit for more intensive oxygen therapy methods. High-flow nasal oxygen therapy (HFNO) proved to be sufficient in 58% of those patients, while 42% required invasive mechanical ventilation<sup>203</sup>. The percentage of patients with severe respiratory failure and ARDS treated in inpatient settings ranged between 19.6% and as much as 41%<sup>204,205</sup>.*

### 2.2.1. Risk factors for a severe course of the disease, respiratory failure and death

| Recommendation  |
|---|
| 2.2.1.1. It is recommended that every patient admitted to hospital be assessed regarding risk factors for a severe course of the disease and death. |

#### Justification:

On the basis of an analysis of available publications<sup>206,207</sup>, mainly retrospective observations of patient groups, the following factors contributing to a severe course of the disease have been determined:

- advanced age,
- co-morbidities;
- lesions identified in a chest CT scan performed upon admission,
- leukopaenia and lymphocytopenia

On the basis of an analysis of the available publications, mainly retrospective observations of patient groups, the following factors contributing to death have been determined:

- advanced age,
- co-morbidities,
- neutrophilia,
- high LDH concentration,
- high IL-6 concentration,
- high D-dimer concentration.

## 2.2.2. Passive oxygen therapy

### **Recommendation**

2.2.2.1. Initiating passive oxygen therapy is recommended after clinical evaluation of the patient and measuring oxygen saturation of arterial haemoglobin (SpO<sub>2</sub>) with a pulse oximeter and determining a <90-92% decrease in SpO<sub>2</sub>. [moderate strength of recommendation]

2.2.2.2. It is recommended that patients with hypoxic respiratory failure use passive oxygen therapy with the target SpO<sub>2</sub> within the 92-96% range. [expert consensus]

### **Justification:**

No studies assessing the efficacy of oxygen therapy in COVID-19 patients are available. At the same time, it is known that hypoxaemia constitutes a strong risk factor for mortality, and therefore it is recommended to maintain blood oxygenation, measured by percutaneous saturation of arterial blood, at  $\geq$  92%. However, saturation must not exceed 96%, as studies published over the past few years have demonstrated higher mortality in groups of patients with acute respiratory failure and ARDS treated with a target value > 96-98%. Based on an analysis of available data<sup>208,209,210,211,212</sup>, it is concluded that the optimal SpO<sub>2</sub> value in COVID-19 patients with acute respiratory distress is 94 $\pm$ 2%.

### **Recommendation**

2.2.2.3. It is recommended to use all available interfaces in passive oxygen therapy, from the nasal cannula, through a simple face mask and a Venturi mask, to a non-rebreather mask. The interface should be selected based on which one ensures adequate SpO<sub>2</sub> in the particular case and the patient's tolerability.

### **Justification:**

No studies comparing the efficacy of specific interfaces used in passive oxygen therapy are available. The recommendation is based on their theoretical operation and expert experience.

The basic interface for passive oxygen therapy is the nasal cannula, which, depending on the oxygen flow ranging from 1 to 6L/M, provides from approx. 24% to approx. 40% oxygen in the breathing mixture (FiO<sub>2</sub>). To reduce aerosol spread, the patient can be wearing a surgical mask during oxygen therapy via a nasal cannula. A simple oxygen mask with 5-10L/M flows provides approx. 40-60% of FiO<sub>2</sub>. A Venturi mask ensures an oxygen supply with a stable FiO<sub>2</sub> and due to achieving high flows (approx. 40-50L/M) it is indicated in patients with a high respiratory drive. At the same time, high gas flows create the risk of atomisation of exhaust gas particles over significant distances. A non-rebreather mask allows for achieving the greatest FiO<sub>2</sub> values of approx. 80-95%, which depends on the oxygen supply to the reservoir bag (a minimum of 15 L/M) and a sufficient seal around the patient's nose and mouth. All passive oxygen therapy techniques generate aerosol production and pose a risk of infection, which is why full protection must be worn by the medical personnel when the techniques are applied. (recommendations available below)<sup>213,214</sup>

### 2.2.3. High-flow nasal oxygen therapy and non-invasive ventilation (BiPAP, CPAP)

#### **Recommendation**

2.2.3.1. In patients with high  $\text{FiO}_2$  ( $\geq 40\%$ ) requiring passive oxygen therapy treatment using active oxygen, therapy in the form of high-flow nasal oxygen therapy or CPAP/BiPAP non-invasive ventilation support may be attempted, provided there are no indications for urgent intubation and invasive ventilation.

#### **Justification:**

High-flow nasal oxygen therapy (HFNO) consists in supplying a large oxygen-enriched air flow (maximum flow: 60 L/M, maximum  $\text{FiO}_2$ : up to 1.0) via the patient's nose; the supplied air is maximally saturated with steam and heated to body temperature. HFNO can be considered as an intermediate method between passive and active oxygen therapy, as it is characterised by some features of ventilator therapy: it generates a slight positive pressure in the respiratory tract and reduces the patient's active breathing. No direct evidence assessing the efficacy of oxygen therapy in COVID-19 patients is available. Indirect evidence evaluating the use of this method in treatment of hypoxic respiratory failure was used.<sup>215,216,217,218,219,220,221,222</sup> One randomised study demonstrated that the use of HFNO is associated with reduction of mortality risk in patients with hypoxic respiratory failure (standard therapy vs HFNO [HR=2.01; 95% CI 1.01;3.90]; NIV vs HFNO [HR=2.50 95% CI 1.31; 4.78]).<sup>223</sup> A meta-analysis of 9 RCTs (2,093 patients)<sup>224</sup> has demonstrated that HFNO reduced the risk of intubation and ICU admission when compared to conventional oxygen therapy.

Non-invasive ventilation (NIV), understood as supplying positive pressure to the respiratory tract without the need for intubation, is not a recommended method of treating acute hypoxemic respiratory failure in the course of pneumonia or ARDS, as the risk of failure is high (approx. 50%).<sup>225</sup> Nonetheless, in view of the indirect evidence<sup>226</sup> on the reduction of the risk of intubation in patients with mild ARDS, this treatment can be carried out provided that the following conditions are met: the healthcare professionals have experience in the use of NIV, the patient's vital signs can be constantly monitored, in case the patient's condition deteriorates, access to rapid intubation and invasive ventilation is ensured. Delaying intubation due to prolonged use of NIV is a strong factor impacting the risk of mortality. The NIV treatment effectiveness indicators are: reducing breath frequency, reducing shortness of breath, improving the oxygenation index ( $\text{PaO}/\text{FiO}$  or  $\text{SpO}/\text{FiO}$ ).

#### **Recommendation**

2.2.3.2. The use of interfaces which cover the patient's mouth and nose, as well as respiratory systems which minimise the risk of infecting the healthcare professionals is recommended. Experts are of the opinion that this risk becomes greater in the following order: helmet, dual-limb non-vented face mask, single-limb non-vented face mask, vented face mask.

#### **Justification:**

In the case of using non-invasive ventilation (NIV) in patients with acute hypoxemic respiratory failure, the use of nasal masks is not recommended due to the very probable leakage through the mouth. The interface of choice is a mask covering both the mouth and the nose. Three such mask types are available: oronasal, full face (covering also the eyes) and helmet. Considering the possibility of ensuring a tight fit at high therapeutic pressures, long duration of the therapy and the spraying range, the helmet

is the optimal interface. In addition, a meta-analysis of controlled trials<sup>227</sup> demonstrated greater efficacy of the helmet compared to other interfaces in terms of mortality and the need for intubation. In the absence of this interface, a face mask should be used. Even so, the respiratory system should be composed in a manner minimising the risk of spreading aerosol from the patient's respiratory tract. Study results demonstrate that during non-invasive ventilation, aerosol can be spread up to 1 m.<sup>228,229,230,231,232,233</sup>

## 2.2.4. Monitoring

### **Recommendation**

2.2.4.1. During high-flow nasal oxygen therapy or non-invasive ventilation, the possibility of constant monitoring of vital functions and assessing the patient's condition every 1-2 hours should be ensured. Due to the risk of rapid clinical deterioration and aggravation of respiratory failure, the NEWS2 scale is recommended (Annexes no. 4 and 5) to monitor patients.

### **Justification:**

Monitoring the patient is necessary due to the risk of rapid clinical deterioration and the severity of respiratory failure, which would indicate the need for intensifying the treatment (intubation, invasive ventilation) if no decision has been made regarding whether to take such actions. It has been demonstrated that delayed intubation due to ineffective NIV is associated with an increased risk of death.<sup>234</sup>

The NEWS2 scale is a simple and proven scale for assessing the condition of a patient with respiratory failure. It is recommended by the NHS (United Kingdom).<sup>235</sup>

## 2.2.5. Risk of infecting healthcare professionals

### **Recommendation**

2.2.5.1. Special protection measures against infection are recommended: optimal personal protective clothing, negative pressure or adequate ventilation of rooms when performing procedures in the course of which aerosols are generated\*.

### **Justification:**

As demonstrated by experience from China and Hong Kong, when adequate protection is used, the risk of infection is very low.<sup>236</sup> The procedure associated with the greatest risk is intubation as it involves a close and relatively long contact between the doctor's and the patient's airways.

\* Aerosol-generating procedures (AGPs) in oxygen therapy which are associated with a higher risk of contracting a virus include:

- Oxygen therapy using a Venturi mask,
- High-flow nasal oxygen therapy (HFNO),
- CPAP,
- Non-invasive mechanical ventilation (NMV),
- Cardiopulmonary resuscitation (CPR),
- Endotracheal intubation and extubation,
- Self-inflating bag resuscitation (AMBU),

- Endotracheal tube suction using an open suction system,
- Suction of the upper respiratory tract,
- Bronchoscopy and ENT procedures related to the upper respiratory tract requiring suctioning,
- High frequency oscillatory ventilation (HFOV).<sup>237</sup>

## 2.3. Intensive care

### Authors' remarks

*These recommendations were created based on a discussion about the existing guidelines and recommendations on how to proceed with COVID-19 patients, held between invited experts. Given the fact that in the vast majority of cases, the strength of recommendations is very low, the expert panel recommends constant monitoring of new reports on optimal procedures in order to increase the safety of patients and of the healthcare personnel, as well as to improve treatment results. The algorithm of proceeding in the case of identifying clinical manifestation of hypoxia in COVID-19 patients, which constitutes an annex to this document (Annex no. 6), is an integral part of the proposed recommendations. This chapter is dedicated to Intensive Care Units.*

### 2.3.1. Intensive respiratory care

| Recommendation  |
|---|
| 2.3.1.1. Initiating passive oxygen therapy is recommended after clinical evaluation of the patient and measuring oxygen saturation of arterial haemoglobin (SpO <sub>2</sub> ) with a pulse oximeter and determining a <90-92% decrease in SpO <sub>2</sub> . [moderate strength of recommendation] |

#### Justification:

In Guan 2020, the authors demonstrated that 41% of COVID-19 patients (including over 70% of patients in a severe condition) required oxygen therapy.<sup>238</sup> In LOCO2, the authors of the study demonstrated that in ARDS patients, SpO<sub>2</sub> values lower than the target values (88–92%) are associated with a higher risk of death (RD 14% [95% CI 0,7; 27,2], p=NDA.) than in the arm with higher target SpO<sub>2</sub> values (≥96%).<sup>239</sup>

| Recommendation   |
|--|
| 2.3.1.2. The use of continuous SpO <sub>2</sub> measurement and striving to maintain SpO <sub>2</sub> values in the range of 92-96% are recommended in patients treated with passive oxygen therapy [low strength of recommendation] |

#### Justification:

In Chu 2018, meta-regression analysis showed a linear relationship between higher SpO<sub>2</sub> values and the risk of in-hospital death (regression coefficient at 1.25 [95% CI 1– 1.57], p = 0.008) and a higher risk of death during the 30-day follow-up (regression coefficient 1.17 [95% CI 1.01; 1.36], p = 0.0052).<sup>240</sup> In LOCO2, the authors of the study demonstrated that in ARDS patients, SpO<sub>2</sub> values lower than the target values (88–92%) are associated with a higher risk of death (RD 14% [95% CI 0,7; 27,2], p=NDA.) than in the arm with higher target SpO<sub>2</sub> values (≥96%).<sup>241</sup> Considering the risks associated with very high SpO<sub>2</sub> targets and high costs of the increased risk of oxygen depletion, the SSC 2020 guidelines set out a strong recommendation against maintaining SpO<sub>2</sub> targets above 96%. Target SpO<sub>2</sub> at 92-96% was also indicated as optimal.<sup>242</sup>

| <b>Recommendations</b>  |
|---|
| 2.3.1.3. The following escalation of passive oxygen therapy is recommended to increase FiO <sub>2</sub> : first, a nasal cannula should be used (O <sub>2</sub> flow up to 5 L/min, corresponding to FiO <sub>2</sub> □ 0.4), followed by a Venturi mask (oxygen flow adapted to the nozzle, maximum achievable FiO <sub>2</sub> 0.6) and a reservoir mask (O <sub>2</sub> flow up to 15 L/min, maximum possible FiO <sub>2</sub> □ 1.0) [expert consensus] |
| 2.3.1.4. In cases when, in order to maintain the SPO <sub>2</sub> value at >92%, the patients require passive oxygen therapy devices, supplying the inhaled oxygen fraction (FiO <sub>2</sub> )> 0.4, considering indications for mechanical ventilation is recommended. [expert consensus]   |
| 2.3.1.5. During passive oxygen therapy, i.e. a method improving oxygenation, the patient should be lying face down. [expert consensus]  |
| 2.3.1.6. Due to the fact that the use of high-flow nasal oxygen therapy (HFNO) and non-invasive ventilation (NIV) may be associated with an increased risk of infecting the staff, it is recommended that this form of therapy be carried out by experienced healthcare professionals with the use of optimal equipment (interface). [expert consensus]   |
| 2.3.1.7. In patients with hypoxemia in the form of tachypnoea at >35 breaths per minute, decreased SpO <sub>2</sub> value at <90%, deteriorated communication with the patient, persisting despite passive oxygen therapy, tracheal intubation and connecting a ventilator should be considered [expert consensus]  |
| 2.3.1.8. HFNO and NIV may be considered in patients with respiratory failure symptoms despite adequate passive oxygen therapy, and if a temporary delay in tracheal intubation and connecting to a ventilator are possible. [expert consensus]  |
| 2.3.1.9. It is recommended that HFNO and NIV be used when dedicated devices are available outside the anaesthesiology and intensive care units (ICUs), and when continuous monitoring of the vital functions and assessment of the patient's condition every 1-2 hours are possible [expert consensus]  |
| 2.3.1.10. It is recommended that, in order to minimise airborne transmission during HFNO and NIV therapies, they should be conducted in isolation rooms with negative or neutral pressure, and that the healthcare professionals responsible for the patients use FFP2 or N95 masks. [expert consensus]   |
| 2.3.1.11. Considering early tracheal intubation and connecting a ventilator is recommended if the patient's condition deteriorates during HFNO or NIV, in the form of tachypnoea at >35 breaths per minute, decreased SpO <sub>2</sub> value at <90%, deteriorated communication with the patient. [expert consensus]   |

### **Justification:**

The available information on COVID-19 is currently insufficient and hence focusing on the experience and expertise of specialists and clinical experts became necessary. The recommendations were based on the assessment of the scarce scientific evidence combined with the consensus of a multidisciplinary panel of experts.

| <b>Recommendation</b> |
|-----------------------|
|-----------------------|

|  |
|--|
| 2.3.1.12. Protective lung ventilation with volumes of 4-8 mL/kg of the appropriate body weight and not exceeding the plateau pressure of 30 cmH <sub>2</sub> O is recommended in mechanically ventilated patients. [high strength of recommendation] |
|--|

**Justification:**

There are currently no studies on mechanical ventilation strategies in COVID-19 patients or the effect of limiting plateau pressure in COVID-19 ARDS.

Experts believe that it should be similar to that in for other patients with severe respiratory failure treated in ICUs. Analysis of six randomised trials (1,181 patients) indicated a reduction in mortality when using low-volume lung ventilation (RR 0.73, 95% CI 0.63, 0.85).<sup>243,244,245,246,247,248</sup> Based on available evidence, global guidelines recommend using low V<sub>t</sub> (4-8 mL/kg of body weight in patients with ARDS).<sup>249,250,251</sup>

There is numerous indirect evidence regarding patients with acute respiratory syndrome. A systematic review and meta-analysis of RCTs indicated that the use of lung protection strategies with low volume and plateau pressure at <30 cmH<sub>2</sub>O (9 trials and 1,629 patients) decreased the risk of death (RR 0.80, 95% CI 0.66-0.98).<sup>252</sup> A meta-analysis comparing low and high P<sub>plat</sub> ventilation strategies in patients with ARDS (15 RCTs) showed that short-term mortality was higher in patients whose plateau pressure was at >32 cmH<sub>2</sub>O during the first week of ICU stay (day 1: RR 0.77 [95% CI 0.66-0.89]; day 3: RR 0.76 [95% CI 0.64-0.90]; day 7: RR 0.78 [95% CI 0.65-0.93]).<sup>253</sup>

| <b>Recommendation</b> |
|-----------------------|
|-----------------------|

|  |
|--|
| 2.3.1.13. The use of recruitment manoeuvres which create excessive pressure in the patient's chest, and which in turn may damage the lungs (sighs, temporarily increasing inflationary pressure etc.) is not recommended. [low strength of recommendation] |
|--|

**Justification:**

A systematic review and meta-analysis of 6 randomised trials (1,423 patients) demonstrated that recruitment manoeuvres reduced mortality and the number of emergency interventions and improved saturation without increasing the risk of barotrauma.<sup>254</sup> Eight RCTs (2,544 patients) did not associate recruitment manoeuvres with decreased mortality (RR 0.90, 95% CI 0.78-1.04), however subgroup analysis suggested that traditional recruitment manoeuvres significantly decreased mortality (RR 0.85, 95% CI 0.75-0.97), while recruitment manoeuvres associated with gradual PEEP titration increased mortality (RR 1.06, 95% CI 0.97–1.17).<sup>255</sup>

| <b>Recommendations</b> |
|------------------------|
|------------------------|

|   |
|---|
| 2.3.1.14. Hypercapnia is permissible during mechanical ventilation in order to limit lung damage, provided that arterial blood pH value is maintained at >7.2. [expert consensus] |
|---|

|   |
|---|
| 2.3.1.15. Intravenous administration of sodium bicarbonate to correct severe respiratory acidosis is not recommended due to the risk of aggravating hypercapnia. [expert consensus] |
|---|

**Justification:**

The available information on COVID-19 is currently insufficient, which has made necessary to take into account the experience and expertise of specialists and clinical experts. The recommendation was

based on the critical assessment of the scientific evidence collected, combined with the consensus of a multidisciplinary panel of experts.

| <b>Recommendation</b>  |
|--|
| 2.3.1.16. Positive end-expiratory pressure (PEEP) values should be determined based on the ARDS-NET table (Annex no. 7) in order to reduce the risk of atelectasis and lung hyperinflation. [expert consensus] |

**Justification:**

After increasing PEEP, the physicians should monitor the patients for barotrauma. It is important to note that a higher value of positive end-expiratory pressure may lead to a higher P<sub>plat</sub> value, which, at >30 cmH<sub>2</sub>O, is associated with certain risks, as well as certain benefits. Physicians can use the ARDS-NET protocol to determine the optimal PEEP value.<sup>256</sup>

| <b>Recommendation</b>   |
|---|
| 2.3.1.17. In the case of deep hypoxaemia, defined as a sustained PaO <sub>2</sub> /FiO <sub>2</sub> <150 mmHg index, prone positioning is recommended (preferably – several hours per day and repetition of the session over consecutive days in case of achieving improved oxygenation). [high strength of recommendation] |

**Justification:**

As indicated in Cornejo 2013, the prone position theoretically increases the homogeneity of ventilation by reducing lung deformation.<sup>257</sup> This may reduce the differences in intrapulmonary pressure between the dorsal and abdominal sections, further compensating for lung compression<sup>258</sup> and improving perfusion<sup>259</sup>.

| <b>Recommendation</b>  |
|--|
| 2.3.1.18. If, despite sedation, dyssynchrony with ventilator is observed, which makes it impossible to effectively achieve reduction of respiratory volume or resistant hypoxaemia and/or hypercapnia, the use of skeletal muscle relaxants in bolus or continuous infusion is recommended. [low strength of recommendation] |

**Justification:**

In patients with ARDS (moderate to severe), most guidelines recommend an infusion of neuromuscular blocking agents (NMBAs). These recommendations were mainly based on pooled estimates from 3 RCTs (431 patients) showing a reduction in mortality within 90 days after NMBA infusion compared to no infusion<sup>260</sup>. However, the results of the ROSE study called the results of previous studies into question. The study randomised 1,006 patients with moderate to severe ARDS who received NMBA infusions for 48h or intermittent NMBA bolus as needed<sup>261</sup>. The study demonstrated that continuous infusion of cisatracurium besilate did not improve the significant results in any patient.

The Surviving Sepsis Campaign guidelines suggest that continuous NMBA infusion should be reserved only for patients at risk of persistent paralysis, where intermittent dosing may be insufficient, such as patients with persistent patient-ventilator dyssynchrony and patients requiring continuous ventilation in

deep sedation, or patients with persistent high plateau pressure. The impact of NMBA on long-term results is unclear<sup>262</sup>.

| <b>Recommendation</b>  |
|--|
| 2.3.1.19. Disconnecting the ventilator system is not recommended due to the risk of contamination, atelectasis and hypoxaemia. If the system needs to be disconnected, clamping the intubation tube and stopping ventilation on the ventilator BEFORE disconnection is recommended. [expert consensus] |

**Justification:**

The available information on COVID-19 is currently insufficient, which has made necessary to take into account the experience and expertise of specialists and clinical experts. The recommendation was based on the critical assessment of the scientific evidence collected, combined with the consensus of a multidisciplinary panel of experts.

| <b>Recommendation</b>   |
|---|
| 2.3.1.20. Using vasodilators on a routine basis is not recommended. [high strength of recommendation] |

**Justification:**

A Cochrane review of 13 randomised trials (1,243 patients) which used nitric oxide in ARDS treatment, however, this did not demonstrate a significant impact on mortality (RR 1.04 [95% CI 0.9–1.19]) and was associated with an increased risk of acute kidney damage (RR 1.59 [95% CI 1.17–2.16]). Nitric oxide inhalations bring a short-term improvement in saturation. A subgroup of studies describing PaO<sub>2</sub> / FiO<sub>2</sub> values (mmHg) within 24 hours after intervention demonstrated a statistically significant difference in favour of nitric oxide, but this difference was no longer visible after 24 hours. No study assessed nitric oxide inhalation as emergency treatment<sup>263</sup>. Due to possible damage from nitric oxide and no clear benefit in terms of mortality, the SSCM panel decided not to recommend the routine use of nitric oxide in patients with ARDS<sup>264</sup>.

## 2.3.2. ECMO

| <b>Recommendation</b>   |
|---|
| 2.3.2.1. If, despite optimal conventional therapy – artificial ventilation using a ventilator (described in the recommendations of the Intensive Care Panel), hypoxaemia with a PaO <sub>2</sub> /FiO <sub>2</sub> <150 mmHg index or respiratory acidosis pH <7.25 and PaCO <sub>2</sub> >60 mmHg persists, implementing ECMO should be considered or an ECMO centre should be contacted for patient transfer. |
| 2.3.2.2. Patients requiring VV-ECMO should be transferred to the centres listed in Table 45 (Annex no. 8) after prior placement arrangement. [expert consensus]   |

**Justification:**

There are no clinical trials on the use of ECMO in COVID-19 patients. Yang 2020 suggests that 11.5% of COVID-19 patients admitted to the ICU received ECMO<sup>265</sup> treatment, however the clinical course and results of these patients have not been published yet.

The Ministry of Health in Saudi Arabia introduced an ECMO programme during the MERS-CoV epidemic. In a retrospective cohort study, a group of 35 patients with MERS-CoV and refractory hypoxaemia, who received VV ECMO, had lower in-hospital mortality (65 vs. 100%,  $p=0.02$ )<sup>266</sup>. Nonetheless, given its retrospective nature, this study is characterised by a high risk of selection error.

Only two RCTs assessed ECMO in comparison with conventional mechanical ventilation in severe ARDS. The guidelines published in 2017 do not provide specific guidance on the use of ECMO and recommend further testing<sup>267</sup>. Although the latest randomised trial (EOLIA) was discontinued earlier due to the burdensomeness of treatment<sup>268</sup>, a re-analysis using the Bayesian approach offered the possibility of a better interpretation of the results, suggesting lower mortality in severe ARDS associated with the use of ECMO<sup>269</sup>. A recent systematic review of two RCTs (429 patients) demonstrated a reduction in mortality within 60 days with the use of ECMO (RR 0.73, 95% CI 0.58-0.92), however, the risk of haemorrhage was greater<sup>270</sup>.

**Recommendations**

2.3.2.3. It is recommended to use the general principles of treatment management for the qualification and treatment of VV- ECMO as described in the “Updated protocol of treatment in patients requiring the use of extracorporeal membrane oxygenation (ECMO) for the treatment of acute respiratory failure in adults” (document published in Anaesthesiology and Intensive Care, 2017; 2: 92-104) [expert consensus]

**Justification:**

The available information on COVID-19 is currently insufficient, which has made necessary to take into account the experience and expertise of specialists and clinical experts. The recommendations were based on the assessment of small scientific evidence combined with the consensus of a multidisciplinary panel of experts.

### 2.3.3. Managing a patient with ARDS: a summary

A summary of recommendations regarding managing patients with COVID-19 and ARDS is presented in the figure below. The recommendations were formulated by an international panel of experts selected by the Surviving Sepsis Campaign subcommittee for COVID-19<sup>201</sup>.

| COVID-19 with mild ARDS   | COVID-19 with moderate or severe ARDS  | Reserve/adjunctive therapy   |
|---|--|--|
| <b>Recommended</b><br>Vt 4-8 mL/kg and Pplat<30 cm H <sub>2</sub> O | <b>To be considered</b><br>Higher PEEP   | <b>Uncertain recommendation</b><br>Antiviral drugs, chloroquine, anti-IL 6   |
| <b>Recommended</b><br>Bacterial infection tests                     | <b>To be considered</b><br>NMBA bolus to facilitate ventilation  | <b>To be considered</b> (in ventilation in prone position, high Pplt, asynchrony)<br>NMBA infusion for 24 h  |
| <b>Recommended</b><br>Target SpO <sub>2</sub> 92-96%                | <b>To be considered</b> (if the patient responds to an increase in PEEP)<br>Traditional recruitment manoeuvres | <b>To be considered</b><br>Ventilation in prone position 12-16h  |
| <b>To be considered</b><br>Restrictive fluid supply strategy        | <b>To be considered</b><br>Ventilation in prone position 12-16h  | (stop in the absence of a quick response)<br>Test inhalation of nitric oxide   |
| <b>To be considered</b><br>Empiric antibiotic therapy               | <b>To be considered</b> (in ventilation in prone position, high Pplt, asynchrony)<br>NMBA infusion for 24 h    | (follow the local ECMO criteria)<br>V-V ECMO or reference to an ECMO centre  |
| <b>Uncertain recommendation</b><br>Systemic corticosteroids         | <b>Not recommended</b><br>Recruitment manoeuvres with increasing airway pressures                              | ARDS – acute respiratory distress syndrome<br>ECMO – ExtraCorporeal Membrane Oxygenation<br>NMBA – neuromuscular blocking agents<br>PEEP – positive end-expiratory pressure<br>TV – tidal volume |
|   | <b>To be considered</b><br>Brief systemic corticosteroid therapy   |  |
|   | <b>Uncertain recommendation</b><br>Antiviral drugs, chloroquine, anti-IL 6                                     |  |

Figure 3. Summary of recommendations on managing COVID-19 patients with ARDS, based on the Surviving Sepsis Campaign, 2020

## **PART II**

# **PROTECTION OF HEALTHCARE PROFESSIONALS AND ORGANISATION OF WORK**

### 3. Education of healthcare professionals

| <b>Recommendations</b>   |
|--|
| 3.1. The hospital should organise a system designed to train staff in the use of personal protective equipment, including to verify their skills.  |
| 3.2. The training should not cover all available means of personal protective equipment (PPE); instead it should focus specifically on the measures which will be used in the workplace. |

**Note:**

Instructional materials can be found on the Internet; some examples of sources are presented below:

- *Instructional videos of the Cracow Emergency Medical Services concerning the correct use of the Individual Biological Protection Package suit:*
  - <https://www.youtube.com/watch?v=eluftjc8hSU>
  - <https://www.youtube.com/watch?v=UQbiSnry4t4>
- The instructional videos of the NHS showing how to handle personal protective equipment and the correct order of putting it on and taking it off:
  - <https://www.youtube.com/watch?v=oUo5O1JmLH>
  - [https://www.youtube.com/watch?v=kKz\\_vNGsNhc](https://www.youtube.com/watch?v=kKz_vNGsNhc)
  - [https://www.youtube.com/watch?v=-GncQ\\_ed-9w](https://www.youtube.com/watch?v=-GncQ_ed-9w)

### 4. Use of Personal Protective Equipment (PPE)<sup>271</sup>

| <b>Recommendations</b>   |
|--|
| 4.1. The types of personal protective equipment should be chosen depending on the route of transmission. |

**Justification:**

The WHO, CDC and NHS guidelines agree on the fact that the protection of personnel by means of PPEs should be adapted to the route of transmission to which the personnel are exposed: contact, droplet and aerosol.

| <b>Recommendations</b>   |
|--|
| 4.2. It is recommended to identify the aerosol-generating procedures in each ward treating COVID patients, mark zones on the ward plan, make the staff aware of them and place the plan in a location where it is visible to the personnel.  |
| 4.3. The units should be divided into three zones: <ul style="list-style-type: none"><li>• red zone – intended for patients with a suspected/confirmed SARS- CoV-2 infection; the personnel should always use personal protective equipment (this zone is further divided into a droplet transmission risk area and an aerosol generation area),</li></ul> |

- orange zone – intended for putting on/taking off personal protective equipment required in the red zone,
- green zone – intended for patients without a confirmed/suspected COVID-19 infection.

**Note:**

Aerosol-generating procedures (AGP):

- Tracheal intubation and extubation,
- Self-inflating bag resuscitation (AMBU),
- Intubation tube suction using an open suction system,
- Suction of the upper respiratory tract,
- Bronchoscopy and laryngological procedures requiring suction in the upper respiratory tract,
- Endoscopy,
- Operations with high-speed and dust-generating equipment,
- Some dental procedures (high-speed drills),
- Non-invasive ventilation,
- High frequency oscillatory ventilation (HFOV),
- Oxygen therapy with a Venturi mask,
- Inducing cough and sputum,
- High-flow nasal oxygen (HFNO),
- CPAP,
- Cardiopulmonary resuscitation,
- Nasopharyngeal swabs,
- Nebulisation, aerosol therapy.

Areas of increased frequency of aerosol-generating procedures (AGP):

- Intensive care units,
- Post-anaesthesia care units which provide mechanical ventilation and VIV,
- Accident and Emergency Units,
- Wards where non-invasive ventilation is carried out,
- Dental surgery offices,
- Bronchoscopic and endoscopic labs.

**Recommendations**

4.4. The types of personal protective equipment should be chosen depending on the transmission route.

**Note:**

The "bare below the elbow" principle should apply, men should shave or trim their facial hair in a way that allows for the fitting of FFP2-3 class filtering half-mask, chosen on the basis of the fitting test. Protection against droplet infection also protects against contact infection, aerosol protection also protects against droplet and contact infection. To protect against droplets, the plastic apron and gloves should be changed between seeing individual patients. For additional protection against fluids (e.g. secretions), a plastic apron or an additional barrier apron should be worn over the waterproof long sleeve apron. The plastic apron and the gloves should be changed after each contact with the patient.

**Table 43. PPE depending on the route of transmission**

| <b>PPE adapted to the route of transmission</b> | <b>For patients treated as COVID+</b>          | <b>Single case</b>   | <b>Continuous work</b>   |
|---|--|--|--|
| <b>Contact protection</b>                       | > 2 m distance from the patient                | Gloves<br>Plastic apron<br>Surgical mask*  | Gloves<br>Plastic apron<br>Surgical mask*  |
| <b>Droplet protection</b>                       | < 2 m distance from the patient                | Gloves<br>Plastic apron<br>Waterproof long sleeve apron under the plastic apron**<br>Surgical mask*<br>+ face visor or goggles | <b>Gloves (a new pair with each patient)</b><br><b>Plastic apron (new with each patient)</b><br>Waterproof long sleeve apron under the plastic apron**<br>Surgical mask*<br>+ face visor or goggles – all the time           |
| <b>Aerosol protection</b>                       | Active areas and aerosol-generating procedures | Gloves<br>Waterproof long sleeve apron, Goggles, FFP3*** filtering mask or similar, face visor                                 | <b>Gloves (new with each patient)</b><br><b>Plastic apron (new with each patient)</b><br>Waterproof long sleeve apron under the plastic apron,<br>+ goggles,<br>FFP3*** filtering mask or similar, face visor – all the time |

\* An IIR type fluid-resistant surgical mask, compliant with the European Standard 14683, is required – this mask is not an alternative to an FFP3 class filtering half-mask.

\* Plastic apron – sleeveless polyethylene apron.

Waterproof long sleeve apron – a long sleeve plastic apron, a surgical apron or a suit may be used for this purpose.

FFP3\*\*\* filtering masks called half-masks – compliant with the European Standard EN149 and the European Parliament Regulation 2016/425 or identical.

Eye protection – face visor or goggles. Corrective glasses do not provide sufficient protection. The use of face protection in the form of goggles or face visor should be considered if the activity involves the risk of splashing with blood or other body fluids.

**Table 44. Example of the use of a PPE depending on the area or procedure**

| Way                              | Examples of areas or procedures   | Gloves (to each patient) | Plastic apron (to each patient) | Waterproof long sleeve apron | Surgical mask | FFP3 mask | Goggles or face visor |
|----------------------------------|---|--------------------------|---------------------------------|------------------------------|---------------|-----------|-----------------------|
| <b>Aerosol (continuous work)</b> | Active areas in AGP: ICU, A&E, Wards with NIV and others*                             | +                        | +                               | +                            | -             | +         | +                     |
| <b>Aerosol (single)</b>          | AGP outside the active area*  | +                        | -                               | +                            | -             | +         | +                     |
|                                  | Resuscitation   | +                        | -                               | +                            | -             | +         | +                     |
| <b>Droplet</b>                   | Examination at < 2 m  | +                        | +                               | +                            | +/-**         | +/-**     | +                     |
|                                  | Swabbing  | +                        | +                               | +                            | +             | +         | +                     |
|                                  | Blood sampling (continuous work)  | +                        | +                               | +                            | +/-***        | +/-***    | +                     |
| <b>Others</b>                    | Outside active areas, without physical contact > 2m e.g. collecting a medical history | -                        | -                               | -                            | +             | -         | -                     |

\* The procedures should be grouped.

\*\* A surgical mask – to be decided on according to the risk of aerosol generation, in case of oligosymptomatic patients;

\*\*\* If blood sampling is carried out using a patient separation plate, a surgical mask may be used.

### **Recommendations**

4.5. Detailed rules concerning protection of the personnel, depending on the type of medical procedures carried out and the specific medical specialities, should be sought for in the published guidelines.

**Note:**<sup>5</sup>

Below we present sample sources for guidelines developed by surgeons, cardiologists regarding echocardiography and gastroenterologists.

- Guidelines of the Polish Society of Gastroenterology and of the National Consultant for Gastroenterology concerning the performance of gastrointestinal endoscopy in connection with the COVID-19 epidemic (of 16/03/2020)<sup>272</sup>;
- Guidelines for procedures in treatment units of Multidisciplinary Hospital during COVID-19 pandemic, Mitura K., Myśliwiec P., Rogula W., Solecki W., Jarosław Piotr Furtak J., Kazanowski M., Kłęk S., Nowako M. (of 11.04.2020), developed by an expert team under the auspices of the National Consultant for general surgery prof. Wallner, which presents broad and comprehensive recommendations for surgical procedures (also published in the Polish Journal of Surgery). Recommendations adopted and published on the website of the Video Surgery Section of the Society of Polish Surgeons, approved by the Polish Society of Paediatric Surgery;
- Expert opinion of the Working Group on Echocardiography of the Polish Cardiac Society on performing echocardiographic examinations during the COVID-19 pandemic — Polish Heart Journal<sup>273</sup>.

| <b>Recommendations</b>   |
|--|
| 4.6. In areas where exposure to aerosol-generating procedures is constant, PPEs should be used at all times. |

**Note:**

The length of the continuous working time in PPEs depends on the operating conditions and durability of the individual PPE elements. The duration of continuous use of the filtering half-mask should be in accordance with the manufacturer's instructions. Typically, FFP3 or similar masks should not be used continuously for more than 4-6 hours. At the same time, it is important to reduce staff exposure to aerosol by using barrier solutions, cleaners and air exchangers. In the absence of FFP3 or similar masks, using masks with lower filtering properties should be considered. The length of working time in the suit should not exceed 4 hours of continuous work.

## 5. Modification of personnel actions<sup>274</sup>

| <b>Recommendation</b>   |
|---|
| 5.1. The epidemiological risk for each employee should be assessed by his or her direct manager, in consultation with that person and respecting his or her privacy, and should impact his or her scope of tasks and workplace. |

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<sup>5</sup> We encourage readers of these recommendations to provide their authors with information on other useful guidelines relating to particular medical disciplines. Such information will be included in future versions of the Recommendations.

5.2. Making changes to the work organisation in order to ensure the health safety of patients and personnel and to preserve the patient's right to intimacy is recommended to.

**Justification:**

Transformation of a hospital to a Specialist Infectious Disease Hospital means a period of increased risk of an infection outbreak. Focusing on new aims may reduce vigilance in the area of existing therapeutic activities. Admission of the first patients without all the epidemiological protection issues being resolved can cause the infection to spread throughout the hospital. When developing the principles of in-hospital protection against infections, it is important to remember that the activity of employees outside their workplace constitutes an important risk. The risk of transmission of the infection to the hospital is related to, among other things:

- a) commuting to work by public transport<sup>275</sup>
- b) working in another healthcare facility;
- c) living in one household with a healthcare professional working in another facility<sup>276</sup>;
- d) taking care of a family member with whom one does not live on a daily basis;
- e) disregarding epidemiological principles due to one's personality or emotional problems.

A high sense of responsibility for oneself and others, an advanced age, one's own poor health is a factor that increases caution, reducing the risk of infection.

Changes in the organisation of work aimed at reducing the risk of infection should include, among others:

1. Enforcing the 2-metre distance principle between employees in interpersonal contacts;
2. Verification of staff deployment; introduction of barriers between people sitting in close proximity to one another;
3. Introduction of the principle to keep windows open (at all times or as often as possible – at least every hour);
4. Designation of zones where personal belongings, e.g. keys or mobile phones are to be kept;
5. Implementation of non-contact telephone use or use of the hands-free function;
6. Wiping of all touch surfaces at least once every 2 hours, not only by the cleaning staff but also by the healthcare professionals;
7. Obligation to wipe the computer keyboard and mouse once the work is finished. Regular cleaning followed by disinfection performed by cleaning staff using hospital antiviral disinfectants (in case of shortages of hospital disinfectants, the disinfection can be performed with 0.1% sodium hypochlorite (1:50 dilution if an initial 5% household bleach is used)<sup>277</sup>;
8. Measures must be taken to reduce the need for using door handles (also in toilets);
9. Resignation from shared meals;
10. Resignation from mutual preparation of meals or drinks (this principle should also apply to executive secretaries);
11. Setting out lines defining the 2-meter distance from employees' workstations;
12. Elimination of collective attendance lists in favour of separate lists for small teams or, if possible, remote signing of attendance lists;
13. Using personal pens;

14. Reducing the circulation of paper documents to a minimum;
15. Separation building entrances for different groups of personnel and patients.

| <b>Recommendations</b> |
|------------------------|
|------------------------|

|   |
|---|
| 5.3. Continued teamwork of persons who object to the safety rules should be reconsidered. |
|---|

## 6. Shift work

| <b>Recommendations</b> |
|------------------------|
|------------------------|

|  |
|--|
| 6.1. A shift work system at the Units should be developed. |
|--|

**Note:**

Changes in the provisions of civil law contracts of contract workers may be considered, including “idle time pay” understood as a period of periodical refraining from work, and at the same time being on stand-by and ready to take up work immediately, as well as quarantine time related to contact in the treatment / rehabilitation facility.

Working on a weekly basis (work week/break week) as part of the shift work system could be considered. The same work organisation may also apply to nursing and auxiliary personnel. Employees should not be on duty during the break week. The change of cycle should be planned in the middle of the week if possible. Testing for SARS-CoV-2 before returning to work after a break may be considered.

| <b>Recommendations</b> |
|------------------------|
|------------------------|

|   |
|---|
| 6.2. The tests should be performed on any employee with any symptoms suggesting an infectious background of unclear aetiology. Detection of such an infection should result in immediate withdrawal from work. The tests for healthcare professionals should be performed in a different location than the patients' tests. |
|---|

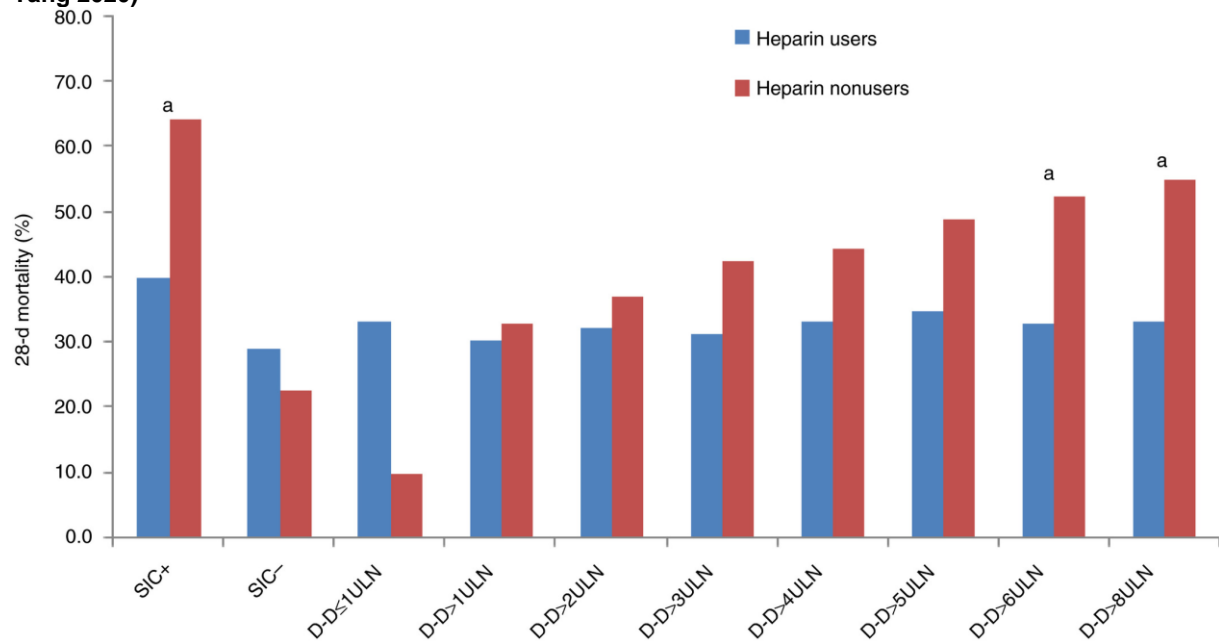
## Annexes

### Annex no. 1 (to “Pharmacotherapy”)

| Basic list           | Additional list      |
|----------------------|----------------------|
| chloroquine          | azvudine             |
| hydroxychloroquine   | baloxavir marboxil   |
| lopinavir/ritonavir  | danoprevir           |
| remdesivir           | darunavir            |
| tocilizumab          | triazavirin          |
| favipiravir          | umifenovir           |
| oseltamivir          | ribavirin            |
| azithromycin         | carriomycin          |
| convalescents plasma | dihydroartemisinin   |
|                      | interferon           |
|                      | corticosteroids      |
|                      | fingolimod           |
|                      | leflunomide          |
|                      | thalidomide          |
|                      | opaganib             |
|                      | ruxolitinib          |
|                      | verdinexor           |
|                      | adalimumab           |
|                      | camrelizumab         |
|                      | eculizumab           |
|                      | mepolizumab          |
|                      | siltuximab           |
|                      | secukinumab          |
|                      | tranilast            |
|                      | novaferon            |
|                      | jakotinib            |
|                      | pirfenidone          |
|                      | bevacizumab          |
|                      | ACE-2 (recombinant   |
|                      | human angiotensin-   |
|                      | converting enzyme 2) |

### Annex no. 2 (to “Pharmacotherapy”)

**Chart: 28-day mortality percentage rates in patients stratified in terms of SIC and D-dimer levels (source: Tang 2020)**



### **Annex no. 3 (to “Pharmacotherapy”)**

Case series of patients receiving lopinavir/ritonavir in COVID-19, with the number of patients exceeding 10, are presented below.

**Liu 2020<sup>278</sup>** (*Journal Pre-proof*)

Between 22 January and 11 February 2020, 10 patients who tested positive for SARS-CoV-2, were checked for eligibility. These patients were admitted to a clinic at Xixi Hospital (hospital dedicated to COVID-19 treatment, Hangzhou) or were transferred in an ambulance from other hospitals in Hangzhou and isolated in a ward with negative pressure rooms.

#### **Results**

The median age of 10 patients (6 women) was 42 years (IQR, 34–50). With the exception of the cases listed below, the quality of the patients’ medical history was adequate. Patient 3 suffered from hypertension and cardiovascular disease and was taking metoprolol and nifedipine. Patient 7 had a chronic liver disease and was taking tenofovir. Nine patients were non-smokers. Patient 7 was a current tobacco user who smoked 20 cigarettes per day for 20 years.

#### **Symptoms**

Cough and fever were observed in most patients (mainly low fever, with temperature ranging from 37.3 to 38.0). Four patients had symptoms of productive cough (white phlegm) and sore throat. Three patients reported headache and nausea. One patient experienced tightness in chest (patient 7). None of the patients had rhinitis, stiffness, diarrhoea or dyspnoea. Leukopaenia and lymphopaenia were observed in two patients. Five patients (patients 1, 2, 3, 6 and 8) developed a serious disease (resting oxygen saturation at less than 93% or arterial oxygen pressure at <60 mm Hg or respiratory rate at more than 30 times per minute), three (patients 1, 2 and 3) were transferred to Zhejiang University Hospital for further treatment. Seven patients (patients 4, 5, 6, 7, 8, 9 and 10) were cured and discharged on 6, 8, 11, 2, 3, 2 and 7 February, respectively. Two patients with a severe condition pre-admission (patients 1 and 2) had multiple symptoms (cough, white phlegm, headache, nausea and fever). Of all the listed patients, patient 7 had only one symptom (tight chest), and developed anxiety following admission. Five patients had not been treated before the onset of symptoms. The results of cardiovascular, abdominal and neurological examinations were normal in all patients, taking into account their medical history.

#### **Treatment and results**

The median time between the onset of symptoms and the start of the treatment was five days (IQR, 3–6). All patients were treated using combination therapy (lopinavir, LPV, 400 mg every twelve hours) and interferon  $\alpha$ 2b inhalations (5 million U twice daily) or LPV monotherapy (patient 7 only). Before the start of treatment, patients 1, 2, 4, 6 and 8 received antibiotics for three days (median, IQR: 2–4). However, it did not alleviate fever or cough.

The median observation time was 13 months (IQR, 4–17). All patients received oxygen inhalation through a nasal cannula, except for patient 7.

Patients 1 and 2 experienced severe digestive disorders (diarrhoea and vomiting) and hypokalaemia within four days of treatment (LPV + interferon  $\alpha$ 2b). Combination therapy was replaced with interferon  $\alpha$ 2b inhalations (5 million U twice per day), arbidol hydrochloride (AHG, 0.2 g, three times per day), human immunoglobulin (IVIG, 20 g daily intravenously) and methylprednisolone (40 mg, every twelve hours). However, the clinical symptoms and radiography were indicative of deterioration. Patient 3 had complex underlying diseases combined with mycoplasma pneumonia. Due to clinical deterioration, patients 1, 2 and 3 were transferred to Zhejiang University Hospital within four days.

Among the reported cases, patient 7 developed atypical radiographic features since admission. Opacity in the CT images of patients 4, 5, 9 and 10 persisted after eight, seven, six and seven days, respectively, from the start of combination therapy with LPV.

The next discharged patient (patient 8) had experienced severe diarrhoea, hypokalaemia, respiratory failure on day 4 and hypoproteinaemia on day 5 of taking LPV and interferon  $\alpha 2b$ .

Therefore, Somac (pantoprazole, 1 tablet per day), human albumin solution (HAS, 10 g per day), AHG (0.2 g, three times per day), IVIG (20 g per day) and methylprednisolone (40 mg, every twelve hours) were added to the original treatment regimen. Adverse reactions, complications and opacity in the CT image in patient 8 improved significantly within two days.

Patient 6 discontinued LPV treatment after four days, due to gastrointestinal adverse effects.

The radiographic improvement period was 14 days, longer than in other patients (8 days).

As the SARS-CoV-2 RNA test results were poor, the patient remained in hospital while the remaining six were discharged.

Patient 6's SARS-CoV-2-RNA result was negative on day 18 from admission, later than in the other patients.

The basis for the discharge was the improvement demonstrated in the radiographic results, absence of the virus in the respiration and reduction of fever for at least 3 days.

#### **Study limitations:**

The limitations include: retrospective observation in a single centre, small sample size and short observation time.

### **Wan 2020<sup>279</sup>**

#### **Study design and participants**

All patients were admitted to Chongqing University Three Gorges between 23 January and 8 February 2020. A total of 135 patients with confirmed COVID-19 were included in the study. Clinical results were monitored from 8 February 2020 until the final observation date. The patients were divided into a mild disease arm (including normal and mild) and severe disease arm (including severe and critical).

Of the 135 hospitalised patients, 40 (29.6%) were included in the severe cases arm and 95 (70.4%) in the mild cases arm. The median age of all patients was 47 years (IQR, 36-55), and 72 (53.3%) patients were male. The most common symptoms at the disease onset were: fever (120 [88.9%], mainly mild to moderate, 37.3°C – 38.9°C: 70 [51.9%], 38.1°C – 39°C: 37 [27.4%]), cough (102 [76.5%]), myalgia or fatigue (44 [32.5%]) and headache (24 [17.7%]). The following symptoms were less frequent: sore throat (34 [25.2%]), dyspnoea (18 [13.3%]), diarrhoea (18 [13.3%]), chest tightness and dyspnoea (12 [8.8%]), fear of cold (14 [10.3%]) and sputum production (12 [8.8%]).

The median time from the onset of symptoms to the transfer was 5 days (IQR: 5–13 days). Since almost all COVID-19 patients experienced coughing as the main early symptom, all suspected patients had chest CT scans. Interstitial pneumonia with mainly bilateral involvement and multiple patchy, flocculent or striped shadows of a dull glass type were the typical pulmonary changes in the results.

#### **Organ disorders and basic interventions**

The common complications observed in the 135 patients included ARDS (21 [15.6%]), acute heart damage (10 [7.4%]), acute kidney damage (5 [3.7%]), secondary infection (7 [5.1%]) and shock (1 [0.7%]). All patients received antiviral therapy, i.e. Kaletra (ropinavir+ritonavir) and interferon (135 [100%]), and many patients received antimicrobial therapy (59 [43.7%]) and corticosteroids (36 [26.7%]).

Twenty-seven (67.5%) patients with a severe form of the disease were subjected to non-invasive ventilation. One patient (2.5%) in the severe arm was subjected to invasive mechanical ventilation. In addition, most patients (124 [91.8%]) were treated using traditional Chinese medicine (TCM). As at 8 February 2020, 15 patients (11.1%) were discharged and one patient died. 28-day mortality was at 2.5%. Most patients were treated using a combination of Western medicine and TCM.

### **Limitations**

The limitations stem from the sample size which was relatively small compared to Wuhan, where the disease originated, which may impact the statistics to some extent. Most of the 135 patients were still being hospitalised at the end of the study.

### **Young 2020<sup>280</sup>**

Description of a series of cases concerning the first 18 patients with COVID-19 in Singapore, diagnosed between 23 January and 3 February 2020. The publication includes patients with a molecularly confirmed (rRT-PCR) SARS-Cov-2 infection; the data originate from 4 hospitals in Singapore. The samples (blood, faeces, urine, nasopharyngeal swabs) were collected from patients frequently within 2 weeks from the inclusion, in order to perform rRT-PCR tests for SARS-Cov-2 infection. The median age of all patients was 47 years (range 31-73), men represented 50% of patients.

All patients have been subjected to adjunctive therapy, including oxygen therapy if the saturation dropped below 92%. Patients with clinical symptoms indicating possible non-nosocomial pneumonia were administered a wide spectrum of antibiotics and oseltamivir orally (p.o.). Of the 6 patients who had to receive oxygen, 5 patients received combined treatment with lopinavir (20 mg)/ritonavir (100 mg), twice a day, treatment period up to 14 days. The samples from the respiratory tract were checked daily with the PCR test for SARS-Cov-2 until two negative results were obtained at an interval of over 24 hours.

Of the 5 patients receiving lopinavir/ritonavir, a decrease in oxygen demand was observed in 3 patients (60%) within 3 days of treatment, and in 2 patients (40%) within 2 days the number of copies of the SARS-Cov-2 virus in the nasopharyngeal swab was reduced. In 2 out of 5 patients taking lopinavir/ritonavir, the health condition deteriorated and progressive respiratory failure occurred, in addition, 1 patient required invasive mechanical ventilation. In these two patients, the presence of the SARS-Cov-2 virus was still detectable in the swab.

Of the 5 patients receiving lopinavir/ritonavir, nausea, vomiting and diarrhoea were reported in 4 patients, and in 3 patients abnormal liver tests were reported. Due to the occurrence of adverse events, the planned 14-day treatment cycle was completed by only 1 patient.

## Annex no. 4 (to “Oxygen therapy”)

### NEWS 2 Scale

Chart 1: The NEWS scoring system

| Physiological parameter        | 3     | 2      | 1         | Score 0             | 1               | 2               | 3             |
|--------------------------------|-------|--------|-----------|---------------------|-----------------|-----------------|---------------|
| Respiration rate (per minute)  | ≤8    |        | 9–11      | 12–20               |                 | 21–24           | ≥25           |
| SpO <sub>2</sub> Scale 1 (%)   | ≤91   | 92–93  | 94–95     | ≥96                 |                 |                 |               |
| SpO <sub>2</sub> Scale 2 (%)   | ≤83   | 84–85  | 86–87     | 88–92<br>≥93 on air | 93–94 on oxygen | 95–96 on oxygen | ≥97 on oxygen |
| Air or oxygen?                 |       | Oxygen |           | Air                 |                 |                 |               |
| Systolic blood pressure (mmHg) | ≤90   | 91–100 | 101–110   | 111–219             |                 |                 | ≥220          |
| Pulse (per minute)             | ≤40   |        | 41–50     | 51–90               | 91–110          | 111–130         | ≥131          |
| Consciousness                  |       |        |           | Alert               |                 |                 | CVPU          |
| Temperature (°C)               | ≤35.0 |        | 35.1–36.0 | 36.1–38.0           | 38.1–39.0       | ≥39.1           |               |

Chart 2: NEWS thresholds and triggers

| NEWS score  | Clinical risk | Response                           |
|---|---------------|------------------------------------|
| Aggregate score 0–4                                 | Low           | Ward-based response                |
| Red score<br>Score of 3 in any individual parameter | Low–medium    | Urgent ward-based response*        |
| Aggregate score 5–6                                 | Medium        | Key threshold for urgent response* |
| Aggregate score 7 or more                           | High          | Urgent or emergency response**     |

\* Response by a clinician or team with competence in the assessment and treatment of acutely ill patients and in recognising when the escalation of care to a critical care team is appropriate.

\*\*The response team must also include staff with critical care skills, including airway management.

**Chart 4: Clinical response to the NEWS trigger thresholds**

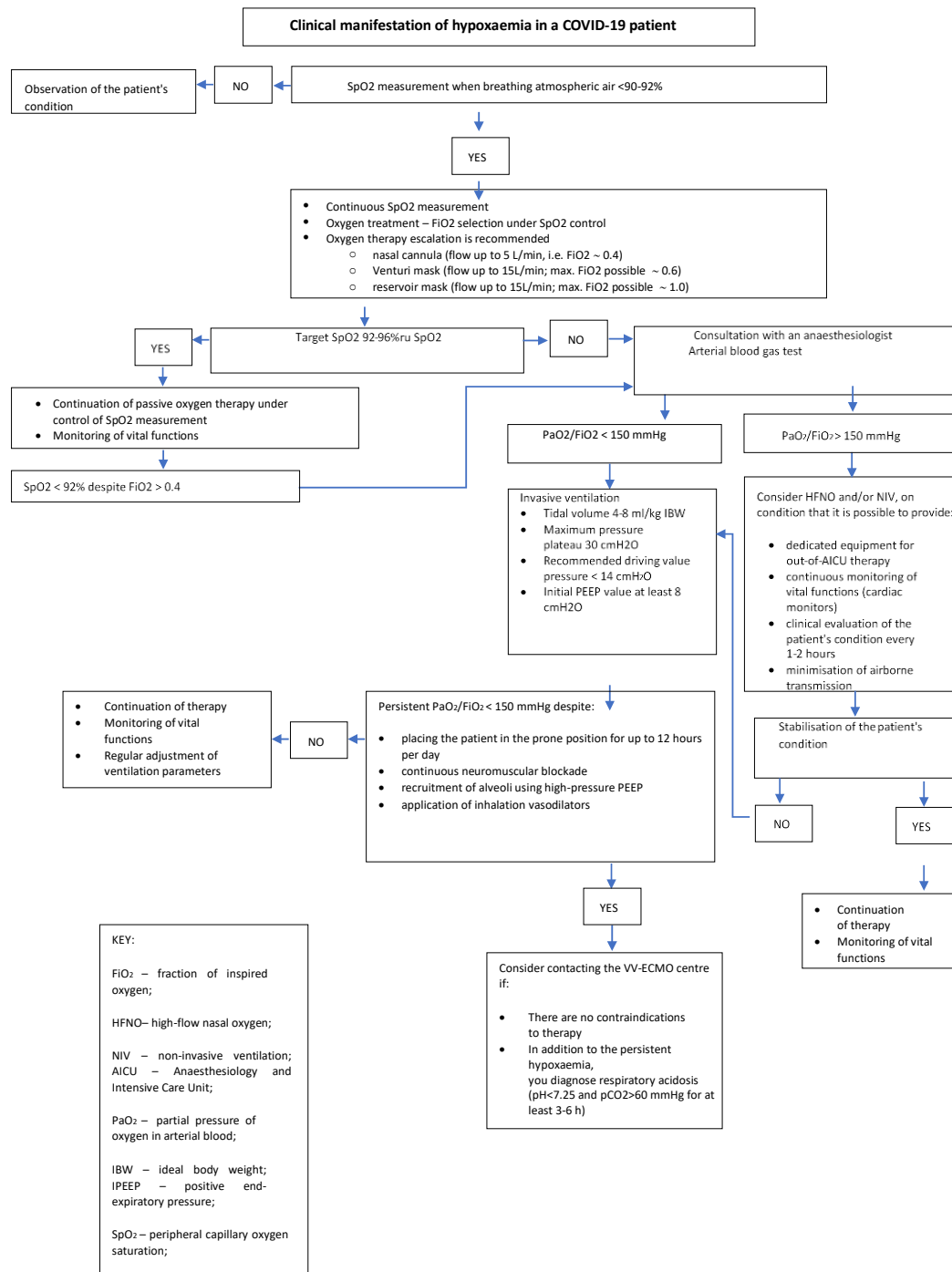
| NEWS score                                      | Frequency of monitoring              | Clinical response  |
|---|--------------------------------------|--|
| 0   | Minimum 12 hourly                    | <ul style="list-style-type: none"> <li>Continue routine NEWS monitoring</li> </ul>   |
| Total 1–4                                       | Minimum 4–6 hourly                   | <ul style="list-style-type: none"> <li>Inform registered nurse, who must assess the patient</li> <li>Registered nurse decides whether increased frequency of monitoring and/or escalation of care is required</li> </ul>   |
| 3 in single parameter                           | Minimum 1 hourly                     | <ul style="list-style-type: none"> <li>Registered nurse to inform medical team caring for the patient, who will review and decide whether escalation of care is necessary</li> </ul>   |
| Total 5 or more<br>Urgent response threshold    | Minimum 1 hourly                     | <ul style="list-style-type: none"> <li>Registered nurse to immediately inform the medical team caring for the patient</li> <li>Registered nurse to request urgent assessment by a clinician or team with core competencies in the care of acutely ill patients</li> <li>Provide clinical care in an environment with monitoring facilities</li> </ul>  |
| Total 7 or more<br>Emergency response threshold | Continuous monitoring of vital signs | <ul style="list-style-type: none"> <li>Registered nurse to immediately inform the medical team caring for the patient – this should be at least at specialist registrar level</li> <li>Emergency assessment by a team with critical care competencies, including practitioner(s) with advanced airway management skills</li> <li>Consider transfer of care to a level 2 or 3 clinical care facility, ie higher-dependency unit or ICU</li> <li>Clinical care in an environment with monitoring facilities</li> </ul> |

# Annex no. 5 (to “Oxygen therapy”) NEWS 2 Scale – Polish version – monitoring card

| NEWS 2 key  |   | FULL NAME            |                   |   |
|---|---|----------------------|-------------------|---|
| 0   | 1   | 2                    | 3                 |   |
|   |   | DATE OF BIRTH        | DATE OF ADMISSION |   |
|   |   | DATE                 | DATE              |   |
|   |   | TIME                 | TIME              |   |
| <b>A+B</b><br>Respirations<br>Breaths/min   | ≥25   |                      | 3                 |   |
|   | 21–24   |                      | 2                 |   |
|   | 18–20   |                      |                   |   |
|   | 15–17   |                      |                   |   |
|   | 12–14   |                      | 1                 |   |
|   | 9–11  |                      | 3                 |   |
| <b>A+B</b><br>SpO <sub>2</sub> Scale 1<br>Oxygen saturation (%)   | ≥96   |                      | 1                 |   |
|   | 94–95   |                      | 2                 |   |
|   | 92–93   |                      | 3                 |   |
|   | ≤91   |                      |                   |   |
| <b>SpO<sub>2</sub> Scale 2</b><br>Oxygen saturation (%)<br>Use Scale 2 if target range is 96–97%,<br>eg in hypoxaemic respiratory failure<br><br>*ONLY use Scale 2 under the direction of a qualified clinician | ≥97... O <sub>2</sub>   |                      | 3                 |   |
|   | 96–96... O <sub>2</sub>   |                      | 2                 |   |
|   | 93–94... O <sub>2</sub>   |                      | 1                 |   |
|   | ≥93... SpF  |                      |                   |   |
|   | 88–92   |                      |                   |   |
|   | 86–87   |                      | 1                 |   |
|   | 84–85   |                      | 2                 |   |
|   | ≤83%  |                      | 3                 |   |
|   | <b>Air or oxygen?</b>   | At Air               |                   |   |
|   |   | O <sub>2</sub> L/min |                   | 2 |
| Device  |   |                      |                   |   |
| <b>C</b><br>Blood pressure<br>mmHg<br>Score uses systolic BP only   | ≥220  |                      | 3                 |   |
|   | 201–219   |                      |                   |   |
|   | 181–200   |                      |                   |   |
|   | 161–180   |                      |                   |   |
|   | 141–160   |                      |                   |   |
|   | 121–140   |                      |                   |   |
|   | 111–120   |                      |                   |   |
|   | 101–110   |                      | 1                 |   |
|   | 91–100  |                      | 2                 |   |
|   | 81–90   |                      |                   |   |
|   | 71–80   |                      |                   |   |
|   | 61–70   |                      | 3                 |   |
|   | 51–60   |                      |                   |   |
|   | ≤50   |                      |                   |   |
| <b>C</b><br>Pulse<br>Beats/min  | ≥131  |                      | 3                 |   |
|   | 121–130   |                      | 2                 |   |
|   | 111–120   |                      |                   |   |
|   | 101–110   |                      | 1                 |   |
|   | 91–100  |                      |                   |   |
|   | 81–90   |                      |                   |   |
|   | 71–80   |                      |                   |   |
|   | 61–70   |                      |                   |   |
|   | 51–60   |                      |                   |   |
|   | 41–50   |                      | 1                 |   |
|   | 31–40   |                      | 3                 |   |
|   | ≤30   |                      |                   |   |
|   | <b>D</b><br>Consciousness<br>Score for HQN<br>level of confusion<br>(No score if awake) | Alert                |                   |   |
|   |   | Confusion            |                   | 3 |
| V   |   |                      |                   |   |
| U   |   |                      |                   |   |
| <b>E</b><br>Temperature<br>°C   | ≥39.1*  |                      | 2                 |   |
|   | 38.1–39.0*  |                      | 1                 |   |
|   | 37.1–38.0*  |                      |                   |   |
|   | 36.1–37.0*  |                      | 1                 |   |
|   | 35.1–36.0*  |                      | 3                 |   |
|   | ≤35.0*  |                      |                   |   |
| <b>NEWS 2 TOTAL</b>   |   |                      | <b>TOTAL</b>      |   |
| Monitoring frequency  |   |                      | Monitoring        |   |
| Escalation of care Y/N  |   |                      | Escalation        |   |
| Initials  |   |                      | Initials          |   |

National Early Warning Score 2 (NEWS 2) © Royal College of Physicians 2017

## Annex no. 6 (to "Intensive care")



**Annex no. 7 ARDSnet Table (to "Intensive care")**

|                  |     |     |     |     |     |     |     |     |
|------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| FiO <sub>2</sub> | 0.3 | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.7 | 0.7 |
| PEEP             | 5   | 5   | 8   | 8   | 10  | 10  | 10  | 12  |

|                  |     |     |     |     |     |       |
|------------------|-----|-----|-----|-----|-----|-------|
| FiO <sub>2</sub> | 0.7 | 0.8 | 0.9 | 0.9 | 0.9 | 1.0   |
| PEEP             | 14  | 14  | 14  | 16  | 18  | 18–24 |

|                  |     |     |     |     |     |     |     |     |
|------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| FiO <sub>2</sub> | 0.3 | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.7 | 0.7 |
| PEEP             | 5   | 5   | 8   | 8   | 10  | 10  | 10  | 12  |

|                  |     |     |     |     |     |       |
|------------------|-----|-----|-----|-----|-----|-------|
| FiO <sub>2</sub> | 0.7 | 0.8 | 0.9 | 0.9 | 0.9 | 1.0   |
| PEEP             | 14  | 14  | 14  | 16  | 18  | 18–24 |

LIST OF ANAESTHESIOLOGY AND INTENSIVE CARE UNITS ABLE TO TREAT ACUTE RESPIRATORY DISTRESS SYNDROME USING VV-ECMO IN PATIENTS WITH COVID-19 (SITUATION AS OF 13.04.2020) (Annex no. 8)

**Table 45. List of Anaesthesiology and Intensive Care Units able to treat acute respiratory distress syndrome using VV-ECMO with COVID-19 patients**

| Name of the centre   | II Anaesthesiology and Intensive Care Clinic SPSK-1 | Pomeranian Centre for Infectious Diseases and Tuberculosis in cooperation with University Clinical Centre Team | Extracorporeal Treatment Centre<br>Cardiac Surgery Clinic<br>Central Clinical Hospital of the MSWiA in Warsaw | Lower Silesian Centre for Heart Diseases | University Hospital in Cracow  |
|--|---|--|---|--|--|
| Address of the centre  | ul. Staszica 16, 20-038, Lublin                     | ul. Smoluchowskiego 18, 80-214, Gdańsk   | ul. Wołoska 137, 02-507, Warsaw   | ul. Kamieńskiego 73A, 51-124, Wrocław    | ul. Jakubowskiego 2, 30-688, Cracow  |
| Phone number to the VV-ECMO coordinator  | 81-5349795  | 58-5844209   | 22-5081704; 22-5081702; 22-5081262  | 71-3209437<br>71-3209438                 | 12-4001887   |
| E-mail address to the VV-ECMO coordinator  | czuczwarm@gmail.com                                 | rlango@gumed.edu.pl<br>wkarolak@gmail.com  | dominik.drobinski@cskmswia.pl<br>ctp@cskmswia.pl  | marcirak@gmail.com                       | konstantys@gmail.com<br><a href="mailto:w.serednicki@hotmail.com">w.serednicki@hotmail.com</a> |
| Number of treatment stations for patients with COVID-19  | 8   | 6  | 10  | 6  | 55   |
| Number of stations to VV-ECMO therapy  | 3   | 3  | 5   | 1  | 4  |
| Possibility to start VV-ECMO therapy in the reporting centre and transport the patient to the centre | YES   | NO   | YES   | NO                                       | NO   |

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