

**National Institute for the Infectious Diseases “L. Spallanzani”, IRCCS
Recommendations for COVID-19 Clinical Management**

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Summary

On January 9 2020, the “World Health Organization” (WHO) declared the identification, by Chinese Health authorities, of a novel coronavirus, further classified as SARS-CoV-2 responsible of a disease (COVID-19) ranging from asymptomatic cases to severe respiratory involvement. On March 9 2020, WHO declared COVID-19 a global pandemic. Italy is the second most affected country by COVID-19 infection after China. The “*L. Spallanzani*” National Institute for the Infectious Diseases, IRCCS has been the first Italian hospital to admit and manage patients affected by COVID-19. Hereby, we show our recommendations for the management of COVID-19 patients, based on very limited clinical evidences; they should be considered as expert opinions, which may be modified according to newly produced literature data.

Introduction

On January 9 2020, the “World Health Organization” (WHO) declared the identification, by Chinese Health authorities, of a novel coronavirus, further classified as SARS-CoV-2. This new virus, initially emerged in the Chinese city of Wuhan in December 2019, led to a sharply spreading outbreak of human respiratory disease (COVID-2019), both within People's Republic of China and in several other countries worldwide. On March 9 2020, WHO declared COVID-19 a global pandemic. Currently, Italy is the second most affected country by COVID-19 infection after China. The first autochthonous infection case was confirmed in Italy on February 21 2020 and up to now (March 12), 12462 cases with 827 deaths have been registered in Italy. Considering the recent evolution of Italian epidemiologic picture, many health-care facilities will be likely in charge of managing patients affected by COVID-19 in the next days. The “*L. Spallanzani*” National Institute for the Infectious Diseases, IRCCS has been the first Italian hospital to admit patients affected by COVID-19. Therefore, it will be useful to share the protocol for the clinical management of COVID-19 confirmed cases, applied within our Institute, in order to support other facilities that may have a limited experience in treating COVID-19 patients.

Procedures described in the present document are applied in agreement with the “Regional Network for the Infectious Diseases”, the “Regional Hospital and Medical Specialties Network” and with the active cooperation of the “Regional Agency for the Health Emergencies – ARES 118”. This latter is in charge for the response to the territorial health emergencies and for the transport of patients within the hospital network.

Recommendations described within this document are based on very limited clinical evidences. Consequently, they should be considered as expert opinions, which may be modified according to newly produced literature data.

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Table 1. Modified Early Warning Score (MEWS)

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1. COVID-19 case definition:

1.1 Suspected case

a. A person with an acute respiratory infection (defined as acute onset of at least one of the following sign/symptoms: fever, cough, respiratory difficulty breathing)

and without another etiology which completely explains the clinical presentation

and history of travels/stay in countries where there has been documented local transmission* within the 14 days preceding symptoms onset

OR

b. A person with an acute respiratory infection

and

a history of close contact with a probable or confirmed COVID-19 case in the within the 14 days preceding symptoms onset

OR

c. A person with a severe respiratory infection (fever and at least one sign/symptom of respiratory disease e.g. cough or difficulty breathing)

and

who require hospital admission

and

another etiology which completely explains the clinical presentation

In the setting of primary care/AE department in countries/areas where autochthonous transmission has been observed, all patients with signs/symptoms of acute respiratory infection should be considered as suspected cases.

* According to WHO reports available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>

1.2 Probable case

A suspected case in which the result of SARS-COV-2 Real Time PCR performed at Regional reference laboratories is doubtful or not conclusive or the result of a pan-coronavirus test is positive.

1.3 Confirmed case

A person with laboratory confirmation of SARS-CoV-2 infection, performed at National Reference Laboratory (“Istituto Superiore di Sanità”), irrespective of clinical signs and symptoms.

2. Clinical management based on case severity

2.1 Asymptomatic or mild infection

Cases not presenting any clinical feature suggesting a complicated course of the infection. Main goals of clinical management are:

- 1) Application of strict measures of infection prevention
- 2) Clinical monitoring, in order to early identify possible signs of clinical worsening

The application of strict measures of infection prevention should be applied for all patients with suspected or confirmed infection, regardless of clinical severity.

- **Characteristics:**
 - No symptoms or mild upper respiratory tract manifestations; stable clinical picture
- **Minimal additional microbiologic diagnostics:**
 - Influenza virus detection and/or respiratory agents multiplex PCR on single rhinopharyngeal swab sample
 - SARS-CoV-2 serology if available
- **Clinical monitoring:**
 - Periodic clinical re-evaluation (once/work shift; thrice/day)
 - Periodic vital signs recording (blood pressure, heart rate, respiratory rate, SpO₂, GCS, body temperature) (once/work shift, thrice/day)
- **Virologic monitoring:**
 - SARS-CoV-2 RT-PCR performed on rhinopharyngeal swab every 48-72 hours until persistently negative
- **Diagnostic imaging:**
 - unnecessary
 - in case of cough and/or clinical examination suggesting possible lung involvement, perform chest X-ray
- **Antiviral therapy:**
 - none
- **Supportive therapy:**

- Symptoms control

2.2 Stable patient presenting with respiratory and/or systemic symptoms

(e.g. MEWS clinical deterioration score <3)

Individuals presenting COVID-19 clinical symptoms or signs. Considering the burden of clinical symptoms and the higher risk for complications, the goals of clinical management are, in addition to the ones stated for the asymptomatic patients:

- 1) Closer monitoring of clinical conditions and analytical data
- 2) Strategy aimed at accelerating viral clearance, through use of potentially efficacious experimental antiviral drugs

• Characteristics:

- prostration, severe asthenia, high fever ($> 38^{\circ}\text{C}$) and/or persistent cough,
- clinical or radiological signs of lung involvement
- no clinical or laboratoristic parameters of clinical severity and/or respiratory impairment

• Additional microbiologic diagnostics:

- Influenza virus detection and/or respiratory agents multiplex PCR on single rhinopharyngeal swab sample
- SARS-CoV-2 serology if available
- urinary *L. pneumophila* and *S. pneumoniae* antigen detection
- in case of availability of samples representative of lower respiratory tract (e.g. sputum), perform gram stain and culture; avoid aerosol-generating procedures to induce sputum, because of the higher infectious risk for healthcare workers
- in case of fever ($> 38^{\circ}\text{C}$), perform at least 2 blood cultures, possibly before starting new antimicrobial therapies

• Clinical monitoring:

- Periodic clinical re-evaluation (once/work shift; thrice/day)
- periodic vital signs recording (blood pressure, heart rate, respiratory rate, SpO_2 , GCS, body temperature) (once/work shift, thrice/day), in order to early identify a possible rapid worsening of respiratory functions requiring an increase of the level of care

- arterial blood gas analysis monitoring (mainly between 5th and 7th day or if clinical worsening), to be evaluated together with the intensive care specialist in charge
- **Virologic monitoring:**
 - SARS-CoV-2 RT-PCR performed on rhinopharyngeal swab every 48-72 hours until persistently negative
- **Imaging diagnostics:**
 - Chest X-ray: useful as a first-line radiological examination, for the follow-up and for a rapid assessment of certain pulmonary/thoracic emergencies. Quick and easy to perform; in case of necessity, it can be performed using portable systems.
 - Chest computed tomography, without contrast: high sensitivity in identifying and quantifying lung parenchymal involvement. No absolute indication at this stage of the disease, but highly valuable, together with blood gas analysis, to predict clinical worsening. Chest CT report should be evaluated together with the intensive care specialist in charge
- **Antiviral therapy:**
 - **Lopinavir/ritonavir*** 200/50 mg tablets, 2 tablets q12h, during 14 days
and
Hydroxychloroquine phosphate** 400 mg tablets, 1 tablet q12 as loading dose, followed by 200 mg tablets, 1 tablet q12, during 10 days, or **Chloroquine phosphate**** 250 mg tablets, 2 tablet q12, during 10 days
 - * Alternatively to Lopinavir/ritonavir, **Darunavir** 600 mg tablets, 1 tablet q12 plus **Ritonavir** 100 mg tablets, 1 tablet q12, during 14 days.
 - ** Before chloroquine and hydrossichloroquine administration, G6PD deficiency test should be performed.
- **Supportive therapy:**
 - symptomatic
 - oral rehydration
 - consider antimicrobial therapy (broad spectrum-empiric or based on microbiological results)
 - prompt availability of O₂, in case of necessity

2.3 Patient affected by respiratory symptoms, clinically unstable, not in critical conditions (e.g.: MEWS clinical deterioration score 3-4)

Patients presenting severe respiratory conditions related to SARS-CoV-2 infection and/or to its complications. Adjunctive goals of clinical management at this stage are:

- 1) strict monitoring, especially between 5th and 7th day since symptoms onset, in order to ensure an immediate life support and an increase of the level of care, whenever required.
 - 2) maintenance of an adequate peripheral oxygenation, through O₂ administration
 - 3) use of potentially efficacious antiviral experimental drugs, aimed at rapidly reducing viral replication
 - 4) empirical or targeted treatment of possible bacterial co-infections;
 - 5) prompt assessment of the need of drugs aimed at modulating the immune and inflammatory response, in order to counteract the evolution to ARDS
- **Characteristics:**
 - Clinical and/or laboratoristic evidence of worsening of gas exchange (mild-to-moderate dyspnoea, high respiratory rate, shortness of breath, low peripheral SpO₂ or altered arterial blood gases while breathing room air), without any critical or warning signs (severe respiratory failure, respiratory distress, consciousness disorders, hypotension, shock)
 - **Additional microbiologic diagnostics:**
 - Influenza virus detection and/or respiratory agents multiplex PCR on single rhinopharyngeal swab sample
 - SARS-CoV-2 serology if available
 - Urinary *L. pneumophila* and *S. pneumoniae* antigen detection
 - In case of availability of sample representative of lower respiratory tract (e.g. sputum), perform gram stain and culture; avoid aerosol-generating procedures to induce sputum, because of the higher infectious risk for healthcare workers
 - In case of fever (> 38°C), perform at least 2 blood cultures, possibly before starting new antimicrobial therapies
 - Other eventual diagnostics based on the specific clinical picture (e.g. HIV test, *P. jirovecii* detection on respiratory fluids, MRSA on nasal swab, etc...)
 - **Clinical monitoring:**
 - Strict clinical re-evaluation

- Strict periodic vital signs recording (blood pressure, heart rate, respiratory rate, SpO₂, GCS, body temperature), in order to early identify a possible rapid worsening of respiratory functions, requiring an increase of the level of care
- arterial blood gas analysis monitoring (mainly between 5th and 7th day), to be evaluated together with the intensive care specialist in charge
- Consultation with an intensive care specialist
- **Virologic, immunologic and biochemical monitoring:**
 - SARS-CoV-2 RT-PCR performed on rhinopharyngeal swab every 48-72 hours until persistently negative
 - IL-6 plasma levels
 - D-dimer, ferritin, fibrinogen, C-reactive protein, tryglicerides, lactate dehydrogenase (LDH)
- **Imaging diagnostics:**
 - Chest X-ray: useful as a first-line radiological examination, for the follow-up and for a rapid assessment of certain pulmonary/thoracic emergencies. Quick and easy to perform; in case of necessity, it can be performed using portable systems
 - Chest computed tomography, without contrast: high sensitivity in identifying and quantifying lung parenchymal involvement. To be performed in every patient affected by lung involvement causing respiratory failure. Use of contrast only in case of specific clinical questions (e.g. pulmonary embolism). Chest CT report should be evaluated together with the intensive care specialist in charge
 - Ecocardiography: indicated in case of suspected hearth failure as a contributing factor to lung involvement/respiratory failure
- **Antiviral therapy:**
 - **Remdesivir^o (GS-57324)**, once daily intravenously: 200 mg loading dose, followed by 100 mg daily maintenance dose, during 10 days, or (if Remdesivir not available) **Lopinavir/ritonavir* 200/50 mg tablets, 2 tablets q12h, during 28 days**
and
Hydroxychloroquine phosphate 400 mg tablets, 1 tablet q12 as loading dose, followed by 200 mg tablets, 1 tablet q12, during 10 days, or Chloroquine phosphate** 250 mg tablets, 2 tablet q12, during 10 days**
and

Tocilizumab[^] 8 mg/kg (maximum 800 mg/dose), single dose intravenously (1-hour infusion); in absence or with poor clinical improvement a second dose should be administered after 8-12 hours

* Alternatively to Lopinavir/ritonavir, **Darunavir** 600 mg tablets, 1 tablet q12 plus **Ritonavir** 100 mg tablets, 1 tablet q12, during 14 days.

** Before chloroquine and hydroxychloroquine administration, G6PD deficiency test should be performed

° Do not co-administrate Remdesivir with lopinavir/ritonavir, due to possible drug interactions

[^] Tocilizumab administration should be guided by the presence of 1 or more of following selection criteria: a) PaO₂/FiO₂ ratio <300 mmHg; b) rapid worsening of respiratory gas exchange with or without availability of non-invasive or invasive ventilation; d) IL-6 levels >40 pg/mL (if not available, see D-dimer levels >1000 ng/mL).

Therapeutic schedule: 2 administrations (each 8 mg/kg, maximum 800 mg). Second administration at 8-12 hours from the first one. Repeat PCR and Ddimer (+/-IL-6) after 24 hours from each administration.

- **Supportive therapy:**

- O₂ administration
- antimicrobial therapy (broad spectrum-empiric or based on microbiological results)
- oral or intravenous rehydration
- consider systemic steroids administration in case of clinical signs suggesting an incipient worsening of respiratory functions (steroids are mandatory if Tocilizumab is used) (methylprednisolone 1 mg/Kg daily intravenously for 5 days, followed by 40 mg daily for 3 days and, lastly, 10 mg daily for 2 days, or dexamethasone 20 mg daily intravenously for 5 days, followed by 10 mg daily for 3 days and lastly 5 mg daily for 2 days)

2.4 **Critical patient (e.g. MEWS clinical deterioration score >4)**

Patient affected by a very severe illness, due to severe respiratory failure or severe impairment of other vital functions. Main goals during this stage are, in conjunction to the procedures described for the unstable patient:

- 1) Life support and intensive monitoring
- 2) Rapid recognition and immediate management of complications
- 3) Active search for adjunctive or alternative diagnosis
- 4) Use of drugs aimed at reducing the impact of inflammatory response to ARDS

- **Characteristics:**

- Acute respiratory distress syndrome (ARDS)
- Severe respiratory failure, respiratory distress
- Hypotension - Shock
- Multiorgan failure (MOF)
- Consciousness impairment

- **Additional microbiologic diagnostics:**

- Influenza virus detection and/or respiratory agents multiplex PCR on single rhinopharyngeal swab sample
- SARS-CoV-2 serology if available
- Urinary *L. pneumophila* and *S. pneumoniae* antigen detection
- In case of availability of samples representative of lower respiratory tract (e.g.: sputum), perform gram stain and culture; avoid aerosol-generating procedures to induce sputum, because of the higher infectious risk for healthcare workers
- In case of fever (> 38°C), perform at least 2 blood cultures, possibly before starting new antimicrobial therapies
- Other eventual diagnostics based on the specific clinical picture (e.g. HIV test, *P. jirovecii* detection on respiratory fluids, MRSA on nasal swab, etc...)

- **Clinical monitoring:**

- Strict monitoring and intensive care, starting from patients with moderate ARDS, according to Berlin definition ($100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$)

- **Virologic, immunologic and biochemical monitoring:**

- SARS-CoV-2 RT-PCR performed on rhinopharyngeal swab every 48-72 hours until persistently negative

- SARS-CoV-2 RT-PCR performed on samples representing lower respiratory tract, using the same timing
- IL-6 plasma levels
- D-dimer, ferritin, fibrinogen, C-reactive protein, tryglicerides, lactate dehydrogenase (LDH)
- **Imaging diagnostics:**
 - Chest computed tomography, without contrast: high sensitivity in identifying and quantifying lung parenchymal involvement. To be performed in every patient affected by lung involvement causing respiratory failure. Use of contrast only in case of specific clinical questions (e.g. pulmonary embolism). The exam is required by the intensive care specialist in charge
 - Ecocardiography: indicated in case of suspected hearth failure as a contributing factor to lung involvement/respiratory failure
- **Antiviral therapy:**
 - **Remdesivir[°] (GS-57324)**, once daily intravenously: 200 mg loading dose, followed by 100 mg daily maintenance dose, during 10 days, or (if Remdesivir not available) **Lopinavir/ritonavir*** 200/50 mg tablets, 2 tablets q12h, during 14 days
and
Hydroxychloroquine phosphate** 400 mg tablets, 1 tablet q12 as loading dose, followed by 200 mg tablets, 1 tablet q12, during 10 days, or **Chloroquine phosphate**** 250 mg tablets, 2 tablet q12, during 10 days
and
Tocilizumab[^] 8 mg/kg (maximum 800 mg/dose), single dose intravenously (1-hour infusion); in absence or with poor clinical improvement a second dose should be administered after 8-12 hours

* Alternatively to Lopinavir/ritonavir, **Darunavir** 600 mg tablets, 1 tablet q12 plus **Ritonavir** 100 mg tablets, 1 tablet q12, during 14 days.

** Before chloroquine and hydrossichloroquine administration, G6PD deficiency test should be performed

° Do not co-administrate Remdesivir with lopinavir/ritonavir, due to possible drug interactions

^ Tocilizumab administration should be guided by the following selection criteria: a) PaO₂/FiO₂ ratio <300 mmHg; b) rapid worsening of respiratory gas exchange with or without availability of non-invasive or invasive ventilation; d) IL-6 levels >40 pg/mL (if not available, see D-dimer levels >1000 ng/mL).

- **Supportive therapy:**

- Gold standard: early protective mechanical ventilation as recommended for patients affected by ARDS sustained by viral interstitial pneumonia
- Antimicrobial therapy (broad spectrum-empiric or based on microbiological results)
- Intensive care and monitoring as indicated by hospital protocols
- Systemic steroid therapy in case of ARDS/severe respiratory failure (steroids are mandatory if Tocilizumab is used) ((methylprednisolone 1 mg/Kg daily intravenously for 5 days, followed by 40 mg daily for 3 days and, lastly, 10 mg daily for 2 days, or dexamethasone 20 mg daily intravenously for 5 days, followed by 10 mg daily for 3 days and lastly 5 mg daily for 2 days)
- consider ECMO in case of refractory hypoxemia despite invasive mechanical ventilation. Indication is given by the intensive care specialist in charge, according to ECMONET criteria and to ECMO regional center

3. ARDS criteria (Berlin definition – 2012 + Kigali adaptation for low resource settings):

- **Onset:** new or worsening respiratory symptoms within one week of known clinical insult
- **Chest imaging** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules
- **Origin of oedema:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor is present
- **Oxygenation** (adults):
 - Mild ARDS: $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ (with PEEP or CPAP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated)
 - Moderate ARDS: $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated)
 - Severe ARDS: $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated)

- When PaO₂ is not available, SpO₂/FiO₂ ≤315 suggests ARDS (including in non-ventilated patients)
- **Oxygenation** (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO₂):
 - Bilevel NIV or CPAP ≥5 cmH₂O via full face mask: PaO₂/FiO₂ ≤ 300 mmHg or SpO₂/FiO₂ ≤264
 - Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5
 - Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3
 - Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3

4. Antiviral/Immunological Therapy

There are currently no medications or vaccines proven to be effective for COVID-19. Some either old or new agents have been proposed and explored for treatment of COVID-19 but clinical trials are still underway. Up to now, the only available data are based on anecdotal experiences and expert opinions.

4.1 Chloroquine and hydroxychloroquine

Chloroquine is an old and widely used anti-malarial drug and it is also efficacious as an anti-inflammatory agent for rheumatologic disease. Earlier studies have demonstrated a potential antiviral effect of this drug against SARS and avian influenza H5N1.

Mechanism of Action

It has been postulated that antiviral action of chloroquine may depend by several mechanisms such as the change of cell membrane pH which is necessary for viral fusion and the interference with glycosylation of viral proteins. Hydroxychloroquine, an analogue of chloroquine, has been proved to have similar if not better in-vitro efficacy on SARS-Cov-2.

Available data on SARS-COV2

A recent study has demonstrated in-vitro efficacy of chloroquine and remdesivir in inhibiting replication of SARS-COV2. Moreover, emerging reports from China suggests that chloroquine has shown a superiority in reducing both the severity and the duration of clinical disease without significant adverse events in almost one hundred patients. In light of this results, an expert consensus group in China has recommended chloroquine for COVID_19 treatment.

Dosage

The recommended dosage for SARS-CoV-2 infection is chloroquine 500 mg bid or hydroxychloroquine 200 mg bid for 10 days in combination with another antiviral agent (Lopinavir/ritonavir or Remdesivir).

Adverse Events/Cautions:

Serious adverse effects may include: QT prolongation & torsades de pointes, reduction in seizure threshold, anaphylaxis or anaphylactoid reaction, neuromuscular impairment, neuropsychiatric disorders (potential to increase delirium), pancytopenia, neutropenia, thrombocytopenia, aplastic anemia, hepatitis.

Common adverse reactions: nausea/vomiting, diarrhea, abdominal pain, visual disturbance, headache, extrapyramidal symptoms

It is important to check G6PDH before starting treatment and during treatment to monitor complete blood count, QT interval.

Contraindicated in: Porphyria, G6PD deficiency, epilepsy, heart failure, recent myocardial infarction.

4.2 Lopinavir/ritonavir

Lopinavir/ritonavir is a well-known protease inhibitor which has been widely used for many years for the treatment of HIV infection. Compared to remdesivir, lopinavir/ritonavir has the advantage that it's widely available and has an established toxicity and drug-drug interactions profile. Its antiviral action against coronavirus infections has been previously demonstrated both in-vitro and in-vivo (animal and human data) in studies conducted on SARS (in combination with ribavirin) and MERS infection. Moreover, a randomized clinical trial (RCTs) on lopinavir/ritonavir combined with IFN β use in MERS infection is currently ongoing [MIRACLE Trial].

Mechanism of Action

Lopinavir act its antiviral activity by inhibiting viral replication. As in HIV infection, ritonavir only acts boosting lopinavir plasma levels.

Available data on SARS-COV2

Although only limited and anecdotal data are available of the clinical efficacy of lopinavir/ritonavir in COVID-19 infection so far, it seems to rapidly reduce SARS-CoV2 replication. Lopinavir/ritonavir is currently under investigation within several RCTs in China.

Dosage

The recommended dose for COVID-19 is the 400/100 mg bid (the standard dose used for HIV therapy). In case of swallowing difficulties or unconscious patient the oral solution of lopinavir/ritonavir should be administered (tablets cannot be crushed).

Adverse Events/Cautions:

Serious adverse effects may include: Hypersensitivity reaction, angioedema, Stevens-Johnson syndrome and Toxic epidermal necrolysis, EKG alterations (QT prolongation & Torsade de Pointes, AV block, PR prolongation), pancytopenia, Pancreatitis, Hepatotoxicity

Common adverse reactions: gastrointestinal symptoms (nausea/vomiting, diarrhea)

Monitoring transaminase levels during treatment and drug-drug interactions before treatment start.

In the light of the possible shortage of lopinavir/ritonavir stocks due to the increasing prescriptions, we suggest the possible use of darunavir/ritonavir at the dosage of 600 mg ever 12 hours in replacement of lopinavir/ritonavir considering the similar mechanism of action and the optimal safety profile.

4.3 Remdesivir (GS-5734)

Remdesivir is a novel nucleotide analogue currently under evaluation in clinical trials for Ebola infection. Remdesivir has shown clinical an excellent activity against other coronavirus infections (SARS, MERS) both in-vitro and in animal models.

Mechanism of Action

It acts by inhibiting viral polymerase

Available data on SARS-COV2

A recent study exploring in-vitro activity of remdesivir and chloroquine has demonstrated efficacy of the drugs in inhibiting replication of SARS-COV2. A recent case report described the use of remdesivir, requested for compassionate use, in the first patients with COVID-19 in the United States. Two ongoing clinical randomized clinical trials in China are evaluating remdesivir for moderate and severe COVID-19 infections.

To check drug-drug interactions of antiviral therapy please visit the University of Liverpool website: <http://www.covid19-druginteractions.org>

4.3 Tocilizumab

Rationale for the use and mechanism of action:

Tocilizumab (TCZ) is an anti-human IL-6 receptor monoclonal antibody that inhibits signal transduction by binding sIL-6R and mIL-6R. The main approved indication is for rheumatoid arthritis, in association or not with methotrexate.

In 2017, the U.S. Food and Drug Administration approved TCZ for the treatment of cytokine release syndrome (CRS) consisting in a systemic inflammatory response caused by the massive release of pro-inflammatory cytokines in response to iatrogenic (e.g. CAR-t therapies) or infective stimuli.

Available data on SARS-COV2

Although the lack of data on SARS-CoV-2 pathogenesis, studies in China showed a possible correlation of massive inflammation and severe lung damage on the rapid evolution of fatal pneumonia.

Indeed, in COVID-19 patients, significant differences in IL-6 plasmatic levels were observed at different stage of disease with a higher expression in severe cases than mild ones. Moreover, in the biopsy samples at autopsy from a severe COVID-19 patient, histological examination showed diffuse alveolar damage with cellular fibromyxoid exudates and interstitial mononuclear inflammatory infiltrates suggesting severe immune injury.

Despite the lack of clinical trials on TCZ efficacy and safety for COVID-19 treatment, in China TCZ was recently approved for patients affected by severe SARS-CoV-2 pulmonary complications by the National Health Commission of the People's Republic of China.

Preliminary data from an observational study conducted in China on 21 severe cases receiving TCZ, showed an improvement of the clinical and radiological outcome.

Indications

TCZ is a potential treatment strategy in severe and critical COVID-19 patients. In particular, patients who could benefit from TCZ therapy are:

1. Patients with respiratory symptoms, unstable and severe but not in critical conditions (e.g. clinical instability score of MEWS 3-4) with evidence of worsening of gas exchange with mild to moderate dyspnoea, tachypnea, worsening of SpO₂ or arterial blood gas analysis parameters in ambient air (SpO₂ ≤ 93% in ambient air, PaO₂/FiO₂ ≤ 300 mmHg) in the absence of critical manifestations or signs of alarm (severe respiratory failure, respiratory distress, altered state of consciousness, hypotension, cardiovascular shock);
2. Patient with respiratory symptoms in critical conditions (e.g. clinical instability score of MEWS > 4) with evidence of ARDS (from moderate ARDS according to the Berlin

definition: 100 mmHg $<PaO_2 / FiO_2 \leq 200$ mmHg) or severe respiratory failure or evidence of rapid worsening as respiratory distress with the need for mechanical ventilation or the presence of shock or the presence of concomitant organ failure with the need for intensive care monitoring.

Dosage

although the optimal dose and schedule of TCZ for treatment of CRS is not known, the intended posology is 8 mg/kg intravenously (maximum 800 mg/dose) infused over an hour. Additional administration(s) are evaluated on the basis of patient's response to TCZ 8-12 hours apart, in case of:

- Absence/poor clinical improvement or clinical worsening and/or
- Failure in reduction of 50% baseline C-reactive protein (a reliable surrogate marker of IL-6) or failure in normalization and/or
- Failure in reduction in D-dimer, fibrinogen or ferritin levels.

Dosage adjustment is required in relation to blood parameters of liver function and blood count according to the indications specified in the patient package insert.

It is advisable monitoring of the following blood parameters (full blood count including platelet count, ALT/AST, LDH, fibrinogen, D-dimer, ferritin, C-reactive protein and IL-6) at different time points: immediately before 1st infusion, immediately before 2nd infusion, 24h after 2nd infusion, 36h after 2nd infusion.

Adverse events/cautions

Severe life-threatening infections and alterations in blood parameters as ALT / AST >5 ULN, absolute neutrophils count <500 cell/mmc and platelet count <50000 cell/mmc are contraindications for TCZ treatment. Caution is required in special categories: pregnancy/breastfeeding, active/latent pulmonary tuberculosis, bacterial/fungal infections, immune-related rheumatic disease or concomitant therapy with anti-rejection drugs or immunomodulating therapies, hepatopathies (including viral hepatitis). The safety profile of TCZ is well known. In the TQT study, the most common marked laboratory abnormality was low neutrophil counts. Decreases were observed in mean neutrophil counts following single doses of TCZ over the first 2 days post-treatment, reaching a maximum at approximately 24 hours after the infusion. The observed incidence of marked decreases in neutrophil counts increased with the higher dose of TCZ. Thrombocytopenia and increase of liver function tests have also been described.

For more detailed information, the reader should refer to the patient package insert.

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Appendix/Supplementary Tables.

Table 1. Modified Early Warning Score (MEWS)

PHYSIOLOGIC PARAMETHERS (indicate only one value for each factor)							
Vital sign	3	2	1	0	1	2	3
Respiratory rate (bpm)		< 9		9-14	15-20	21-29	≥ 30
Heart rate (bpm)		≤ 40	41-50	51-100	101-110	111-129	≥ 130
Systolic blood pressure (mmHg)	< 70	71-80	81-100	101-199		≥200	
Temperature (°C)		≤ 35 °C		35.1-38.4		≥ 38.4°C	
Neurologic symptoms				Alert	React to voice	React to pain	Unresponsive (GCS < 9)

TOTAL SCORE |__|__|MEWS legend: 0-2 stable, 3-4 unstable, ≥ 5critical

SpO₂ ____ breathing room air |__| during O₂ administration |__| ____ Lt/min

PaO₂/FiO₂ ratio _____

Table 2. Clinical management of COVID-19 cases according to severity of clinical picture

	ILLNESS SEVERITY	SIGNS/SYMPTOMS	DIAGNOSTIC EVALUATION/ MONITORING	ANTIVIRAL/IMMUNOTHERAPY	SUPPORTIVE THERAPY
S T A B L E	<u>Asymptomatic or mild infection</u>	- No symptoms or mild upper respiratory tract manifestations - stable clinical picture	VAE: respiratory agents multiplex PCR on single RP swab sample; SARS-CoV-2 serology [#] C: clinic and vital sign evaluation x 3/day VM: SARS-COV-2 RT-PCR on RP swab every 48-72 h until persistently negative R: generally not necessary- Chest X-ray if cough/symptoms suggesting lung involvement	none	symptoms control
	<u>Stable patient presenting with respiratory and/or systemic symptoms (MEWS<3)</u>	- prostration, severe asthenia, high fever (> 38°C) and/or persistent cough, - clinical or radiological signs of lung involvement - no clinical or laboratoristic parameters of clinical severity and/or respiratory impairment	VAE: respiratory agents multiplex PCR on single RP swab sample; SARS-CoV-2 serology [#] ; urinary Ag for <i>L. pneumophila</i> and <i>S. pneumoniae</i> ; 2 BC if temperature>38°C C: clinic and vital sign evaluation x 3/day; evaluate ABG (5-7 th day or if clinical worsening) VM: SARS-COV-2 RT-PCR on RP swab every 48-72 h until persistently negative R: Chest X-ray (first radiological assessment); Evaluate Chest HRTC (higher sensitivity)	Lopinavir/ritonavir 200/50 mg [^] tablets, 2 tablets q12h, during 14 days AND Hydroxychloroquine phosphate* 400 mg tablets, 1 tablet q12 as loading dose, followed by 200 mg tablets, 1 tablet q12, during 10 days, or Chloroquine phosphate* 250 mg tablets, 2 tablet q12, during 10 days	- symptomatic - oral rehydration - consider broad-spectrum antimicrobial therapy - prompt availability of O ₂ , in case of necessity

<p style="text-align: center;">U N S T A B L E</p>	<p style="text-align: center;"><u>Patient affected by respiratory symptoms, clinically unstable, not in critical conditions (MEWS 3-4)</u></p>	<p>- Clinical and/or laboratoristic evidence of worsening of gas exchange (mild-to-moderate dyspnoea, high respiratory rate, shortness of breath, low peripheral SpO₂ or altered arterial blood gases while breathing room air) - no critical or warning signs</p>	<p>VAE: respiratory agents multiplex PCR on single RP swab sample; SARS-CoV-2 serology[#]; urinary Ag for <i>L. pneumophila</i> and <i>S. pneumoniae</i>; 2 BC if temperature >38°C; Other based on the specific clinical picture C: strict clinic and vital sign evaluation (>3/day); evaluate ABG monitoring VM: SARS-COV-2 RT-PCR on RP swab every 48-72 h until persistently negative; IL-6 plasma levels; D-dimer, ferritin, fibrinogen, C-reactive protein, tryglicerides, LDH R: Chest X-ray (first radiological assessment); Chest HRTC in all patients: evaluate echocardiography[§]</p>	<p>Remdesivir[°] (GS-57324), QD intravenously: 200 mg loading dose, followed by 100 mg daily maintenance dose, during 10 days</p> <p>OR Lopinavir/ritonavir 200/50 mg[^] tablets, 2 tablets q12h, during 14 days (if Remdesivir is unavailable)</p> <p>AND Hydroxychloroquine phosphate* 400 mg tablets, 1 tablet q12 as loading dose, followed by 200 mg tablets, 1 tablet q12, during 10 days, or Chloroquine phosphate* 250 mg tablets, 2 tablet q12, during 10 days</p> <p>AND Tocilizumab[°] 8 mg/kg (maximum 800 mg/dose), single dose intravenously (1-hour infusion); in absence or with poor clinical improvement a second dose should be administered after 8-12 hours</p>	<p>- O2 administration -broad-spectrum antimicrobial therapy -oral or intravenous rehydration - consider systemic steroids administration</p>
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<p style="text-align: center;">C R I T I C A L</p>	<p style="text-align: center;"><u>Patients with severe illness, due to severe respiratory failure or severe impairment of other vital functions (MEWS>4)</u></p>	<ul style="list-style-type: none"> - Acute respiratory distress syndrome (ARDS) - Severe respiratory failure, respiratory distress - Hypotension - Shock - Multiorgan failure (MOF) - Consciousness impairment 	<p>VAE: respiratory agents multiplex PCR on single RP swab sample; SARS-CoV-2 serology[#]; urinary Ag for <i>L. pneumophila</i> and <i>S. pneumoniae</i>; 2 BC if temperature>38°C;</p> <p>Other based on the specific clinical picture</p> <p>C: strict clinic, vital sign and ABG evaluation and intensive care in patients with moderate or more severe grade of ARDS</p> <p>VM: SARS-COV-2 RT-PCR on RP swab every 48-72 h until persistently negative; SARS-CoV-2 RT-PCR performed on samples representing lower respiratory tract, using the same timing</p> <p>IL-6 plasma levels; D-dimer, ferritin, fibrinogen, C-reactive protein, tryglicerides, LDH</p> <p>R: Chest HRTC in all patients: evaluate echocardiography[§]</p>	<p>Remdesivir[°] (GS-57324), QD intravenously: 200 mg loading dose, followed by 100 mg daily maintenance dose, during 10 days</p> <p>OR</p> <p>Lopinavir/ritonavir 200/50 mg[^] tablets, 2 tablets q12h, during 14 days (if Remdesevir is unavailable)</p> <p>AND</p> <p>Hydroxychloroquine phosphate* 400 mg tablets, 1 tablet q12 as loading dose, followed by 200 mg tablets, 1 tablet q12, during 10 days, or Chloroquine phosphate* 250 mg tablets, 2 tablet q12, during 10 days</p> <p>AND</p> <p>Tocilizumab[°] 8 mg/kg (maximum 800 mg/dose), single dose intravenously (1-hour infusion); in absence or with poor clinical improvement a second dose should be administered after 8-12 hours</p>	<ul style="list-style-type: none"> - Gold standard: early protective mechanical ventilation - Broad-spectrum antimicrobial therapy - Intensive care and monitoring as indicated by hospital protocols - Systemic steroid therapy in case of ARDS/severe respiratory failure (steroids are mandatory if Tocilizumab is used) - consider ECMO in case of refractory hypoxemia despite invasive mechanical ventilation.
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Abbreviation: C: clinical evaluation; MAE: Microbiological Additional exams; VM: virologic monitoring; R: radiologic evaluation; RP: rhinopharyngeal; Ag: antigen; BC: blood cultures; ABG: arterial blood gas analysis; HRTC: high resolution CT scan; QD: once daily

if available

[^] Alternatively to Lopinavir/ritonavir, Darunavir 600 mg tablets, 1 tablet q12 plus Ritonavir 100 mg tablets, 1 tablet q12, during 28 days.

* Before chloroquine and hydrossichloroquine administration, G6PD deficiency test should be performed.

§ If heart failure contributing to respiratory symptoms is suspected

[°] Tocilizumab administration should be guided by the following selection criteria: a) PaO₂/FiO₂ ratio <300 mmHg; b) rapid worsening of respiratory gas exchange with or without availability of non-invasive or invasive ventilation; d) IL-6 levels >40 pg/mL (if not available, see D-dimer levels >1000 ng/mL).