

Guidelines for the treatment of people with COVID-19 disease Edition 2.0, 13 March 2020

Italian Society of Infectious and Tropical Diseases

(Note from Karin Leder: I speak zero Italian, so this is only a Google translate version)

Introduction

In February 2020 the emergence of the COVID-19 epidemic (Corona Virus Disease 2019) in Italy and, above all, in Lombardy, with a potential fatal outcome in a significant proportion of cases, determined the need to prepare tools that support clinicians for therapeutic decisions, based on the limited data available in literature. There is no registered molecule for the treatment of COVID-19 infections. However, there are ongoing trials on the use of some antivirals that have shown efficacy on COVID-19 both in vitro than on animal models as well as in anecdotal experiments. Above all, experience can be used resulting from the use of viral agents on viruses belonging to the same family of Betacoronavirus, specifically the viruses responsible for SARS and MERS. The emergency facing the scientific community in addressing the COVID-19 epidemic provides the rationale for the use of antivirals despite the scientific evidence still being preliminary.

Lethality and comorbidity from COVID-19

The Chinese Disease Control and Prevention Center (China CDC) recently released the wider COVID-19 case study, updated to 11 February 2020 (1), complementing other more limited reports from the city of Wuhan in China (2, 3). From what reported in this descriptive analysis, there were 44672 cases ascertained, of which most are in the age group between 30 and 79 years (87%), while a minority are in the extreme age groups (approximately 1% between 1-9 years and 3% ≥ 80 years). The overall lethality rate was 2.3% (1,023 deaths out of 44,672 confirmed cases).

Among the factors determining of the risk of death we report:

- Age: the lethality rate rises to 8% in patients between 70-79 years and can reach 14.8% in those aged ≥ 80 years.
- The presence of comorbidities: lethality rises to 10.5% in patients with cardiovascular disease, 7.3% in diabetics, 6.3% in subjects with chronic respiratory diseases, 6% in hypertensive patients and finally 5.6% in patients oncology.
- The severity of the clinical presentation: 49% mortality in patients defined as critical.

Also in a descriptive study of the clinical-epidemiological characteristics of 41 patients with COVID-19, the prognostic importance of the presence of associated comorbidities is reported (3). Out of the total number of patients ($n = 41$), 8 (20%) were diabetic, 6 (15%) were hypertensive and 6 (15%) had cardiovascular disease. Between these, 13 patients (32%) were conducted in intensive care due to the need for ventilatory support for hypoxemia or respiratory failure. To date, however, uncertainties remain regarding the infection's fatality rate (4). Overall, the lessons

learned from the SARS epidemic of 2003 appeared to be very useful for dealing with the COVID-19 epidemic (5).

Support measures

In general, steroid therapy does not appear to add any clinical outcome benefits in the treatment of COVID-19 infection. Conversely, steroid therapy may slow down clearance of the virus (6).

However, in patients with confirmed ARDS, but NOT with COVID-19 infections, a benefit of low dose dexamethasone for a limited period of time (10 days) in significantly reducing mortality has been described (7). Although it is an indirect evidence, it appears reasonable to consider the use of dexamethasone only in patients with confirmed ARDS and on indication intensivistica.

There is strong evidence that the use of NIV in the treatment of COVID-19 pneumonia is associated with a worse outcome. On this basis, WHO recommends, where possible, to avoid using NIV and adopt instead standards that provide for early intubation. In case of need to use the NIV, this must be employed within an intensive care unit (8).

In light of the expansion of the epidemic, an increasing shortage of beds has occurred in the last period in intensive care which has determined the need for certain types of treatment to be possible run outside of these operating units.

Regarding this, the Working Group is in favor of the use of non-invasive ventilation even outside the intensive care units.

With respect to the use of the steroid (dexamethasone), the working group expresses itself, with caution, on the possibility of use of dexamethasone even outside the intensive care units, in patients without ARDS in oxygen therapy with clinical signs of worsening respiratory failure (score 2) or in patients who require non-invasive ventilation (score 3). The working group recommends extreme attention so that the steroid treatment is prescribed only to patients:

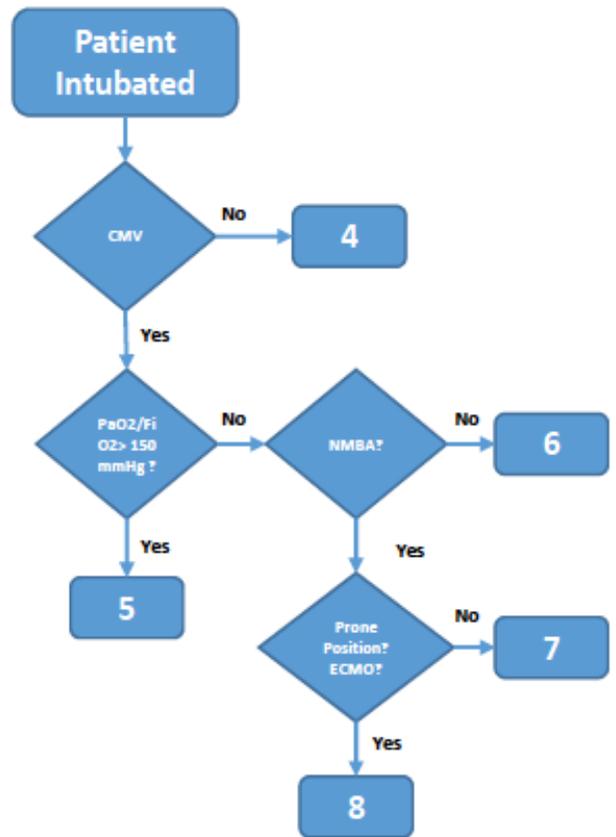
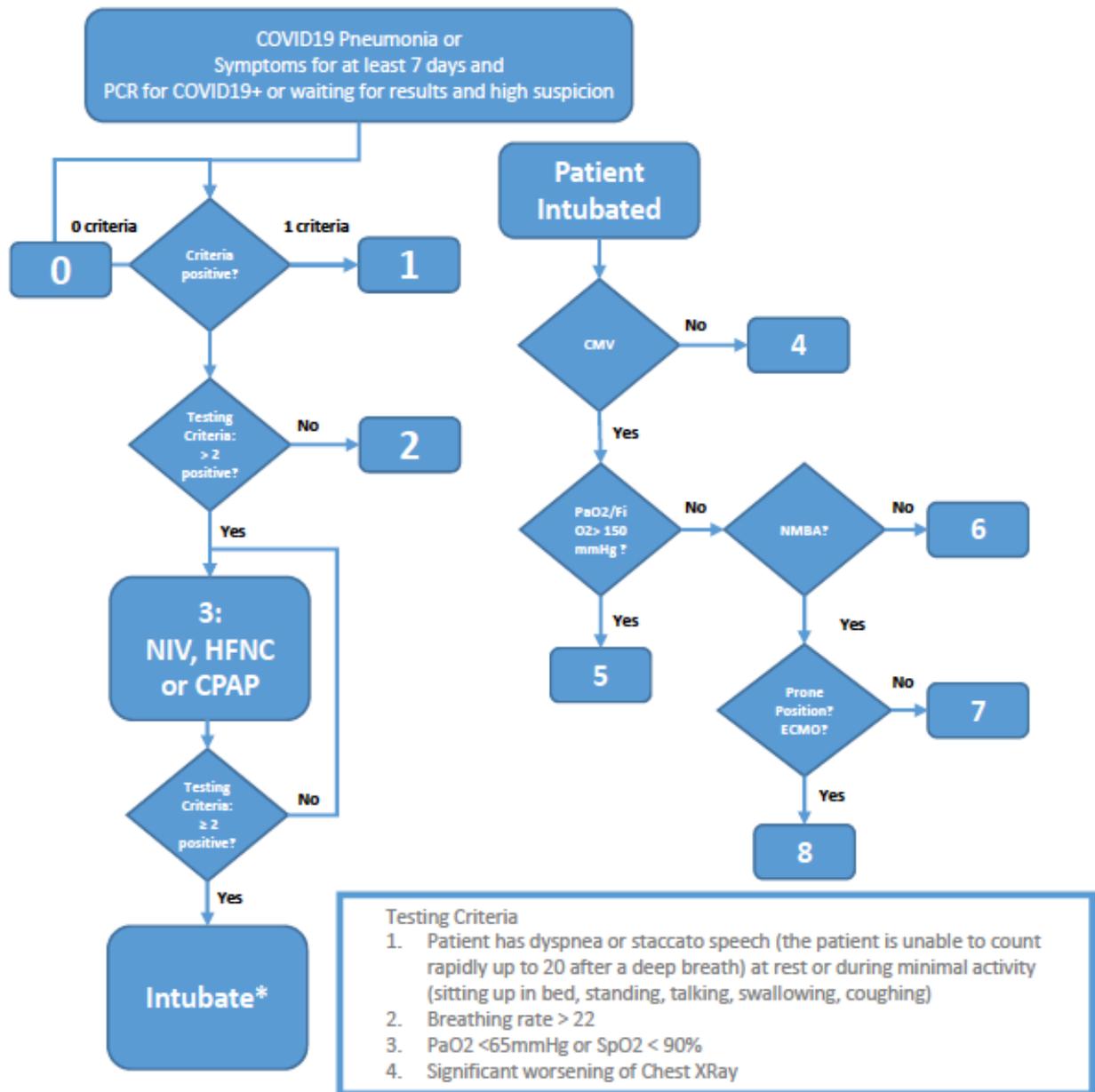
- in which the high viral load phase can be considered finished (e.g. apyretic for > 72h and / or elapsed at least 7 days after the onset of symptoms)
- it can be clinically ruled out that bacterial superinfection is taking place
- only during a worsening of respiratory exchanges and / or significant worsening of the chest radiography (increase in compactness and extension of infiltrates).

Therefore the working group, in collaboration with the resuscitators / intensivists, proposes the following criterion of

stratification of the patient. **Brescia-COVID respiratory severity scale (BCRSS)**

- in which the high viral load phase can be considered finished (e.g. apyretic for > 72h and / or elapsed at least 7 days after the onset of symptoms)
- it can be clinically ruled out that bacterial superinfection is taking place
- only during a worsening of respiratory exchanges and / or significant worsening of the chest radiography (increase in compactness and extension of infiltrates).

Therefore the working group, in collaboration with the resuscitators / intensivists, proposes the following criterion of stratification of the patient. **Brescia-COVID respiratory severity scale (BCRSS)**



0	Keep Patients Monitored with SpO2 and clinical evaluation	Lopinavir/Ritonavir (or boosted/darunavir) + Chloroquine or Hydroxychloroquine Consider
1	Add Oxygen Keep Patients Monitored with SpO2 and clinical evaluation	
2	Keep Patients Monitored with SpO2 and clinical evaluation, perform CXR, Gas Analysis	Dexamethasone*
3	Keep Patients Monitored with SpO2 and clinical evaluation, perform CXR every two days and Gas Analysis twice a day	Request: IL6-CRP-Fibrinogen-ferritin-D-Dimer (start tocilizumab*)
4	Keep Patients in ICU using an internal weaning protocol	
5	Try to minimize sedation (RASS -1 to 0) Perform SBT daily	
6	Try to minimize sedation (RASS -1 to 0)	Tocilizumab + Remdesivir or Lopinavir/Ritonavir or boosted/darunavir + Chloroquine or Hydroxychloroquine
7	Perform Best PEEP and Compliance calculation; Try to suspend NMBA Perform ECHO daily to optimize volume status	
8	High level of complexity	

* Consider age, comorbidity and cognitive decline

Indications for antiviral treatment

Some studies have shown that the earliest possible start of antiviral therapy (both with LPV / r and with remdesivir) reduces the serious complications of the disease (especially acute respiratory failure) (6).

Treatment is indicated in patients with proven virological diagnosis of COVID-19 infection:

- with mild symptoms but with the presence of comorbidity or increased risk of mortality (see above);
- with clinical manifestations of moderate or severe disease.

The working group is in favor of starting antiviral therapy early. In case of delay in diagnosing COVID-19 but with a suggestive clinical picture (interstitial pneumonia) it is reasonable to start the antiviral treatment early even without a swab report (e.g. directly while waiting for the patient in the emergency room).

Pharmacological treatment

Chloroquine

Clinical studies have shown activity in vitro and in animal models of chloroquine phosphate as an antiviral against the SARS virus (9, 10) and avian influenza (11). In fact, it seems that chloroquine can explicate its antiviral efficacy by increasing the endosomal pH necessary for virus / cell fusion guest; moreover, chloroquine appears to interfere with the glycosylation of SARS COV 10 cell receptors.

Chloroquine also has immunomodulatory activity, which could amplify antiviral activity in vivo. The drug has a good penetration into the tissues even after oral administration to a dosage of 500 mg.

In February 2020, a panel of experts in China summarized the results of the use of chloroquine in the treatment of acute COVID-19 infection, suggesting that the use of the drug is associated with an improvement in the rate of clinical success, to the reduction of hospitalization and the improvement of the patient's outcome. The panel recommends using the drug at a dosage of **500 mg BID for 10 days** (12).

Alternatively, if chloroquine is not available, use hydroxychloroquine **200 mg BID**.

The working group speaks out against the possible use of chloroquine / hydroxychloroquine in prophylaxis for COVID-19. At present there is no evidence of efficacy of this drug in disease prophylaxis from COVID-19; therefore this strategy is not recommended.

Lopinavir / ritonavir (LPV / R).

Lopinavir is a known second generation antiretroviral that inhibits viral HIV protease. In combination with ritonavir (antiviral administered at low dosage for the sole potentiating effect of lopinavir) has given important results in reducing morbidity and mortality in patients with HIV / AIDS.

LPV / r is considered to be a promising treatment option for COVID-19 infections, based on the proven efficacy against SARS-COV (in combination with ribavirin) (13). Clinical evidence however, although it has been increasing in the past month, remains limited. The effectiveness clinical LPV / r is suggested by anecdotal cases (14). In a similar way, anecdotal cases suggest how the LPV / r administration is able to reduce the viral load of COVID-19 very quickly (15).

A randomized controlled trial (MIRACLE trial) is currently underway with the aim of verifying the therapeutic efficacy of LPV / RTV + IFN β in patients with MERS-CoV infection (16).

Darunavir ritonavir and darunavir / cobicistat

Ritonavir-boosted Darunavir or cobicistat is a third generation antiretroviral that inhibits the viral protease recommended by the Italian and International Guidelines for the treatment of HIV / AIDS. In fact, in the treatment of this infection it has demonstrated virological suppression power and tolerability greater than lopinavir / ritonavir; however, the evidence that may suggest its use in COVID-19 is very limited. Nonetheless, considering that it is a drug with a mechanism of action very similar to that of lopinavir / ritonavir, it is reasonable to assume that it may exhibit its antiviral efficacy in comparisons of nCoV-19 similarly. A growing lack of lopinavir / ritonavir was also observed due to the increase in prescriptions. Although with less scientific evidence than lopinavir / ritonavir, the working group expressed itself positively on the reasonable use of darunavir 800 mg 1 cp / day + ritonavir 100 mg 1 cp / day or darunavir / cobicistat 800/150 mg 1 cp / day as an alternative in case of lack of lopinavir / ritonavir.

Remdesivir (GS-5734).

Remdesivir is a nucleotide analogue which is incorporated into the nascent viral RNA chain resulting in its premature termination. This mechanism is the basis of its possible effectiveness towards respiratory coronaviruses.

Remdesivir is active in preclinical studies on SARS-CoV and MERS-CoV infections by acting on the viral polymerase of coronavirus (17). In animal models infected with MERS coronavirus, remdesivir appears to have greater efficacy compared to treatment with lopinavir / ritonavir + interferon beta 1 / b.

Recently a North American study group has demonstrated an experimental infection model by MERS in the mouse that the prophylactic use of LPV / RTV-IFN β reduces the viral load but has little impact on disease parameters; in addition, therapeutic use while improving lung function did not reduce the viral replication or the development of severe lung disease (18). In the same study the use of prophylactic and therapeutic remdesivir was shown to be active both in reducing viral load and in improving lung function parameters (18). Another study performed using an infection model MERS-Cov in the macaque confirmed the prophylactic and therapeutic activity of RDV (19).

In an in vitro model of Vero cells infected with the nCoV-2019BetaCoV / Wuhan / WIV / 04/2019 strain, both RDV that chloroquine have been shown to be able to block infection at low concentrations (20).

Two clinical efficacy trials of remdesivir on COVID-19 are currently underway in China:

- for moderate COVID19 infections (NCT04252664 - A Phase 3 Randomized, Double-blind, Placebocontrolled

Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Mild and Moderate 2019-nCoV Respiratory Disease.)

- for severe infections (NCT04257656 - A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Severe 2019-nCoV Respiratory Disease.)

THERAPEUTIC PROTOCOL

- COVID-19 positive patient **asymptomatic or with mild symptoms: (Fever ($> 37.5^{\circ}\text{C}$), cough, symptoms of cooling without dyspnea), age <70 years and without risk factors (COPD, diabetes and heart disease) and negative chest X-ray:**
 - Clinical observation, supportive therapy
- COVID-19 positive patient **with mild respiratory symptoms but aged > 70 years and / or with risk factors (COPD, diabetes and heart disease) or symptomatic or with mild symptoms (Fever ($> 37.5^{\circ}\text{C}$), cough, dyspnoea mild to moderate) and chest x-ray with pneumonia:**
 - lopinavir / ritonavir cps 200/50 mg, 2 x 2 / day (alternatively darunavir 800 mg 1 cp / day + ritonavir 100 mg 1 cp / day or darunavir / cobicistat 800/150 mg 1 cp / day), + chloroquine 500 mg, 1 x 2 / day or hydroxychloroquine cp 200 mg, 1 x 2 / day.

Duration of therapy: from 5 to 20 days, with timing to be established according to clinical evolution

In case of need for **oxygen therapy or rapid clinical worsening (see paragraph "support measures" and COVID respiratory severity scale)** request Remdesivir for compassionate use. At this time suspend LPV / RTV (or DRV / b) and continue with:

- Remdesivir ampoules 150 mg: 1 day 200 mg iv in 30 minutes then 100 mg iv / day for another 9 days in combination chloroquine 500 mg, 1 x 2 / day or hydroxychloroquine 200 mg, 1 x 2 / day (duration of therapy: 5 to 20 days, with timing to be established according to clinical evolution).
 - If patient has BCRSS score ≥ 2 , evaluate: dexamethasone 20 mg / day for 5 days then 10 mg / day for 5 days (on intensivistic indication) and / or tocilizumab (see specific paragraph page 11)
- COVID-19 positive patient with **severe pneumonia, ARDS or overall respiratory failure, hemodynamic failure, need for mechanical (or non-invasive) ventilation:**
 - Remdesivir 1 day 200 mg iv as a charged dose, then 100 mg / day iv (days 2-10) + chloroquine 500 mg, 1 x 2 / day or hydroxychloroquine 200 mg x 2 via SNG (duration of therapy: 5 to 20 days, with timing to be established according to clinical evolution).
 - Until the time of remdesivir availability, undertake LPV / RTV therapy 5 mL x 2 / day (or in alternative DRV / r oral suspension or DRV / c crushed and dispersed) via SNG + hydroxychloroquine 200 mg x 2 via SNG.
 - ARDS patients: 24 hours after ARDS diagnosis: dexamethasone 20 mg / day for 5 days then 10 mg / day for 5 days (on an intensivistic indication) and / or tocilizumab (see specific paragraph page 11)

Drug interactions and drug shortages

The working group recommends maximum attention to possible pharmacokinetic interactions, in particular of lopinavir / ritonavir with other classes of drugs. In case of concomitant intake of other drugs the group recommended to consult the website: <http://www.covid19-druginteractions.org/>

In the presence of drugs contraindicated in use with lopinavir / ritonavir, the working group expresses itself reasonably in favor of the use of chloroquine / hydroxychloroquine only.

The working group recommends the use of lopinavir / ritonavir ed tablet formulation possibly in patients who have difficulty swallowing, switch to the suspended formulation

oral. Lopinavir / ritonavir tablets cannot be crushed. Alternatively, if the oral formulation of lopinavir / ritonavir is not available, it is commercially available a formulation of darunavir in oral suspension (200 ml) to be combined with ritonavir 100 mg sachet.

In the event of a deficiency of darunavir in oral suspension, the working group recalls that the tablets of darunavir and darunavir / cobicistat can be crushed, dispersed and administered via nasogastric tube (21).

Supportive anti-infectious therapy

The choice to add antibiotic (empirical or targeted) and / or antiviral (oseltamivir) therapy should be performed only in the presence of reasonable evidence of bacterial or viral superinfection.

Access to medicines

For the request for use outside the indication of registered drugs (lopinavir / ritonavir and chloroquine or hydroxychloroquine) it is necessary to proceed in accordance with the provisions of the regulations relating to use off-label drugs. For the use of remdesivir, since the drug is not registered in Italy, it is necessary to ask for its use compassionate of the drug, by filling in a special ad personam form, to Gilead Sciences inc. and obtain approval for use by the Ethics Committee.



SIMPLIFIED DOSING REGIMEN

Patient Subset	Clinical Presentation	Supportive Treatment	Antiviral Treatment	Remarks
Asymptomatic patients		None – monitoring	None	
Patients with mild respiratory symptoms	Fever (>37.5 °C), cough, “cold” symptoms without dyspnea	Symptomatic treatment	None	
- Patients with mild respiratory symptoms, but aged >70 years and/or the presence of comorbidities or an increased mortality risk - Patients with moderate respiratory symptoms and/or chest x-ray indicating pneumonia	Fever (>37.5 °C), cough, mild to moderate dyspnea	Symptomatic treatment - Oxygen therapy	Lopinavir/Ritonavir 200/50 mg 2 tablets BID (treatment duration to be determined based on clinical response) + Chloroquine 500 mg BID for 20 days OR Hydroxychloroquine 200 mg BID (treatment duration from 5 to 20 days based on clinical response)	If oxygen therapy is required, it might warrant requesting Remdesivir (refer to “Patients with severe symptoms”)
Patients with severe symptoms	ARDS or Global respiratory failure, hemodynamic decompensation, multi-organ failure	Requires an evaluation by an Intensivist and transfer to the Intensive Care Unit. ARDS patients: 24 hours after ARDS diagnosis: Dexamethasone 20 mg/day for 5 days and then 10 mg/day for 5 days (as indicated by an Intensivist).	Remdesivir (if available) 200 mg/IV loading dose on Day 1 and then a maintenance dose of 100 mg/IV/day from Day 2 to Day 10. + Chloroquine or Hydroxychloroquine (see above) OR Lopinavir/Ritonavir (see above) + Chloroquine or Hydroxychloroquine (see above)	

Use of tocilizumab in patients with severe COVID-19 infection

Rationale

In patients with COVID-19 infection with a serious course, there is a picture of pneumonia that can rapidly degenerate into respiratory failure. The elderly and immunosuppressed subjects are at greatest risk of evolving towards a serious picture of ARDS. A recent study has shown that patients who need hospitalization in resuscitation present a picture of perturbation of the cytokine structure with high levels of IL-6, IL-2, IL-7, IL-10 and TNF- α . Similar changes are observed in release syndrome cytokine (CRS) associated with CAR-T therapy (chimeric antigen receptor (CAR) -T cell therapy) and characterized by fever and multi-organ failure. Cytokines involved in pathogenesis and in clinical manifestations of CRS are IL-6, interferon gamma (IFN-g), tumor necrosis factor alpha (TNF-a) and IL-10 (22). In particular, the central mediator in CRS toxicity is IL-6 (23).

Although immuno-inflammatory therapy is not routinely recommended in COVID pneumonia 19, in consideration of the picture of CRS and of the anatomopathological findings of pulmonary edema and formation of hyaline membranes, a temporally targeted therapeutic approach accompanied by adequate Ventilation support may be of benefit in patients with severe pneumonia who develop ARDS.

Tocilizumab is a drug that blocks the IL-6 receptor. The intravenous formulation has gotten the indication for CRS that occurs during Car-T therapy; given the clinical and cytokine picture in the patients with severe COVID-19 pneumonia, tocilizumab may have a rationale for blocking SIRS caused by the virus in patients with elevated IL-6 levels. In China, in the Anhui Province Hospital, there is a trial course for the use of tocilizumab in the treatment of COVID-19 (ChiCTR 2000029765), the expected dosage it is 8 mg / kg to be repeated after 12 hours.

The dosage used by Xiaoling Xu in a Chinese pilot study (Effective Treatment of Severe COVID-19 Patients with Tocilizumab, in press) was 400 mg iv as a single dose with a possible second dose if clinical response failure; the work shows promising results in 21 patients treated with significant reduction of IL-6 and fever with improvement of lung function.

The recommended posology for the treatment of CRS by intravenous infusion lasting 60 minutes is 8 mg / kg in patients weighing 30 kg or more or 12 mg / kg in patients weighing less than 30 kg. In the absence of clinical improvement in the signs and symptoms of CRS after the first dose, up to 3 additional doses of tocilizumab can be administered. The interval between consecutive doses it must be at least 8 hours.

Patient selection

The working group recommends careful patient selection who can have access to tocilizumab.

Therefore, the working group, in collaboration with the resuscitators / intensivists, proposes the Brescia-COVID respiratory severity scale (BCRSS) as a patient stratification criterion (see also "measures of support "on page 5).

Inclusion criteria

- End of the initial phase of high viral load of COVID-19 (eg apyretic from > 72h and / or elapsed at least 7 days after the onset of symptoms)

- Worsening of respiratory exchanges such as to require non-invasive or invasive support from ventilation (BCRSS score ≥ 3)
- High levels of IL-6 (> 40 pg / ml); alternatively high levels of d-dimer and / or PCR and / or ferritin and / or fibrinogen progressively increasing.

Exclusion criteria

- Age < 18 years
- AST / ALT have values higher than 5 times the normal levels.
- Neutrophil value lower than 500 cells / mmc.
- PLT value lower than 50,000 cells / mmc.
- Documented sepsis from other pathogens other than COVID-19.
- Presence of comorbidities related, according to clinical judgment, to an unfavorable outcome
- Complicated diverticulitis or intestinal perforation
- Skin infection in progress (eg dermohypodermatitis not controlled by antibiotic therapy)
- Immunosuppressive anti-rejection therapy

Proposed therapeutic scheme

A. Maximum 3 infusions at a dosage of 8 mg / kg body weight (maximum dosage per infusion 800 mg)

B. Second infusion 8-12 hours after the first

C. If partial or incomplete clinical response, POSSIBLE third infusion 16-24 hours after first infusion

After 24 hours from the last administration, repeat the plasma dosage of IL-6 and / or D-dimer.

Treatment must be accompanied by antiviral treatment (lopinavir / ritonavir or remdesivir + chloroquine / hydroxychloroquine) and / or steroid (dexamethasone).

Tocilizumab dosages in COVID-19 by body weight

PATIENT WEIGHT	DOSAGE TOCILIZUMAB	Dose range mg / Kg
35-45 kg	320 mg (4 fl da 80 mg)	9,1-7,1
46-55 kg	400 mg (1 fl da 400 mg)	8,7- 7,3
56-65 kg	480 mg (1 fl da 400 mg + 1 fl da 80 mg)	8,6-7,4
66-75 kg	560 mg (1 fl da 400 mg + 2 fl da 80 mg)	8,5-7,5
76-85 kg	600 mg (1 fl da 400 mg + 1 fl da 200 mg)	7,9-7,0
> 86 kg	800 mg (2 fl da 400 mg)	9,3

Availability of the drug

The drug tocilizumab is registered in Italy with different indications, therefore the protocol must be followed company for the use of non-indicated use of registered

drugs and have the patient sign it (except in case of status of necessity) informed consent.

Side effects

S refers to the drug data sheet for anything not included in these recommendations use.

Pregnancy

Since tocilizumab is a monoclonal antibody, it is not a teratogenic drug. One can be observed placental passage from the 16th week of gestation, like all IgG immunoglobulins.

Therefore, the concentration of the drug in the fetal circulation level is higher than that in the maternal circulation towards the end of pregnancy.

The working group therefore recommends considering the risks and benefits of the treatment with the awareness that the newborn exposed in utero in the third trimester of pregnancy has the possibility to result temporarily immunosuppressed pending termination of maternal drug clearance.

Support anti-infectious therapies and reactivation of latent infections

The working group recommends to evaluate well the absence of concomitant systemic infections and eventually set up a broad spectrum preventive antibiotic therapy scheme according to indications clinics, health policies or protocols in use. The working group, although it does not see an increased risk of tuberculosis reactivation in affected subjects from latent tuberculous infection, and considering the need to start treatment in a very short time, recommends performing IGRA tests for tuberculosis and viral markers for the diagnosis of occult hepatitis from HBV .; however, it is not considered necessary to have the results of these tests before starting the treatment.

References

1. (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. China CDC Weekly. Accessed February 20, 2020. <http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51>)
2. (Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China - Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020).
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al; Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.
4. Battegay M, Kuehl R, Tschudin-Sutter S, Hirsch HH, Widmer AF, Neher RA. 2019-Novel coronavirus (2019-nCoV): estimating the case fatality rate: a word of caution. Swiss Med Wkly. 2020;150:w20203.
5. McCloskey B, Heymann DL. SARS to novel coronavirus: old lessons and new lessons. Epidemiol Infect. 2020;148:e22.
6. World Health Organization. Clinical management of severe acute respiratory infection when Novel coronavirus (2019-nCoV) infection is suspected: Interim Guidance. 28 January 2020. WHO/nCoV/Clinical/2020.3).
7. Villar J, Ferrando C, Martinez D, Ambros A, Munoz T, Soler JA, et al.; Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020 Feb 7.
8. World Health Organization. Clinical management of severe acute respiratory infection when Novel coronavirus (2019-nCoV) infection is suspected: Interim Guidance. 28 January 2020. WHO/nCoV/Clinical/2020.3).
9. Savarino A., Di Trani L., Donatelli I., Cauda R. Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect. Dis. 2006; 6: 67–69.
10. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Virol. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread J. 2005; 2, 69.
11. Yan Y, Zou Z, Sun Y, Li X, Xu KF, Wei Y, Jin N, Jiang C. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Cell Res. 2013 Feb;23(2):300-2.
12. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020 Feb 20;43(0):E019.
13. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, et al. HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004 Mar;59(3):252-6.
14. Han W, Quan B, Guo Y, Zhang J, Lu Y, Feng G, et al.. The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019. J Med Virol. 2020 Feb 19.
15. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al.. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. J Korean Med Sci. 2020 Feb 17;35(6):e79.
16. Arabi YM, Asiri AY, Assiri AM, Aziz Jokhdar HA, Allothman A, Balkhy HH, et al.; and the Saudi Critical Care Trials group Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon- β 1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. Trials. 2020 Jan 3;21(1):8.

17. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, Smith EC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio* 2018;9:e00221-18
18. Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020;11:222.
19. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A*. 2020 Feb 13. pii: 201922083.
20. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020 Feb 4.
21. Brown K et al. *Impact of Splitting or Crushing on the Relative Bioavailability of the Darunavir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Single-Tablet* *Clinical Pharmacology in Drug Development* 2019; 8(4):541-548
22. Wang Z, Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. *Biomark Res*. 2018 Jan 22;6:4. doi:10.1186/s40364-018-0116-0. eCollection 2018.
23. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014 Jul 10;124(2):188-95. doi: 10.1182/blood-2014-05-552729. Epub 2014 May 29. Erratum in: *Blood*. 2015 Aug 20;126(8):1048.
Dosage error in article text. *Blood*. 2016 Sep 15;128(11):1533.