Vademecum for the treatment of people with COVID-19. Edition 2.0, 13 March 2020

Lombardy Section of the Italian Society of Infectious and Tropical Diseases

SUMMARY

The spread of COVID-19 epidemic in Italy, and particularly in Lombardy determined the need to standardize the therapeutic approach in order to offer the same indications for all hospitals in Lombardy. However, no specific drug has been previously approved for the COVID-19 treatment.
The Lombardy Section of the Italian Society of Infectious and Tropical Diseases provided this "vademecum" with the aim to explore the current evidence about the drugs likely to be efficacious in the treatment of COVID-19. Moreover, a multidisciplinary group including critical care specialists has been created in order to provide indications about supporting measures and the use of steroids. A new grading scale has been proposed to help patients' stratification according to the severity of the respiratory conditions. Lastly, a collaborating group with immunologists and rheumatologists has been built with the aim of providing some guidance about the use of tocilizumab, a promising option for the treatment of the hyperinflammatory state occurring in most patients affected by COVID-19.

Keywords: vademecum, COVID-19, Lombardy.

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INTRODUCTION

In February 2020, the beginning of the COVID-19 epidemic (Corona Virus Disease 2019) in Italy and, above all, in Lombardy, with the potential of a fatal outcome in a significant proportion of cases, determined the need to support clinician's treatment decisions, based on the few available literature data.

There is no registered treatment for COVID-19 infection. However, there are anecdotal reports and data from studies on the use of antivirals that have shown efficacy on COVID-19 both *in vitro* and in animal models.

Above all, we can learn from experience in the use of antiviral agents on other viruses belonging to the same family of Beta-coronavirus, specifically the viruses responsible for SARS and MERS.

The urgent need to deal with the COVID-19 epidemic that the scientific community is facing provides the rationale for the use of antivirals, despite of the fact that scientific evidence is still preliminary.

Lethality and comorbidity from COVID-19

The Chinese Disease Control and Prevention Center (China CDC) recently published the largest descriptive analysis of COVID-19 cases, updated to the 11th of February 2020 [1]. This study complements a series of other more limited reports from the city of Wuhan in China [2, 3]. In this analysis, they included 44,672 confirmed cases, most of which were in the age groups between 30 and 79 years (87%), while only a minority was 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 patients' characteristics that showed an increased mortality, there were:

- age: the mortality rate increased to 8% in patients between 70-79 years and reached 14.8% in those aged ≥80 years;
- comorbidities: lethality increased to 10.5% in patients with cardiovascular diseases, 7.3% in patients affected with diabetes, 6.3% in subjects with chronic respiratory diseases, 6% in patients with hypertension and finally 5.6% in cancer patients;
- the severity of the clinical presentation: patients defined as critical had a mortality rate of 49%.

Likewise, in another descriptive study on the clinical-epidemiological characteristics of 41 patients with COVID-19, the presence of associated comorbidities was an important prognostic factor [3]. Out of the total number of patients (n=41), 8 (20%) were diabetic, 6 (15%) were hypertensive and 6 (15%) had cardiovascular disease. Thirteen patients (32%) were treated in intensive care unit due to the need for ventilatory support for hypoxemia or respiratory failure.

To date, however, uncertainties remain about the fatality rate [4].

Overall, lessons learned from the SARS epidemic in 2003 appeared to be very useful in dealing with the ongoing epidemic of COVID-19 [5].

Support measures

In general, steroid therapy does not appear to improve clinical outcome in the treatment of COVID-19 infection. On the contrary, it could potentially slow down the clearance of the virus (6). However, a recent study in patients with confirmed ARDS, but NOT with COVID-19 infection, showed that low dose dexamethasone for a limited period of time (10 days) was associated with a significant decreased mortality [7]. Although supportive evidence is on non COVID-19 infected patients, it appears reasonable to consider the use of dexamethasone only in patients with confirmed ARDS and with intensive care team expert advice.

There is strong evidence that the use of non-invasive ventilation (NIV) in the treatment of COVID-19 pneumonia is associated with a worse outcome. On this basis, WHO recommends, where possible, avoiding the use of NIV and implementing standard practice of early intubation. When the use of NIV is needed, they recommend using it within an intensive care unit (ICU) setting [6].

In light of the rapid expansion of the epidemic resulting in an increasing shortage of ICU beds, it will be necessary to carry out certain treatments outside of these units. In this context, the Working Group is in favor of the use of non-invasive ventilation even outside the intensive care unit.

Likewise, the Working Group cautiously favors the possibility of steroids (dexamethasone) use even outside the intensive care units, in selected patients without ARDS, either on oxygen therapy with clinical signs of worsening respiratory failure (score 2) or requiring non-invasive venti-

lation (score 3). The Working Group recommends extreme caution in steroids use, which should be restricted to the following settings:

– the high viral load phase can be considered terminated (e.g. apyretic for >72 h and/or at least 7 days after the onset of symptoms);
– bacterial superinfection can be clinically ruled out;
– worsening of respiratory function and/or significant worsening of the chest X-ray (worsening of consolidation and extension of infiltrates).

Therefore, the Working Group, in collaboration with the critical care teams, proposes the following stratification criteria, Brescia-COVID respiratory severity scale (BCRSS).

Indication to initiate antiviral treatment:

Few studies showed that the early start of antiviral therapy (both with lopinavir/ritonavir and with remdesivir), as soon as possible, reduces the serious complications of the disease (especially acute respiratory failure) [6].

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

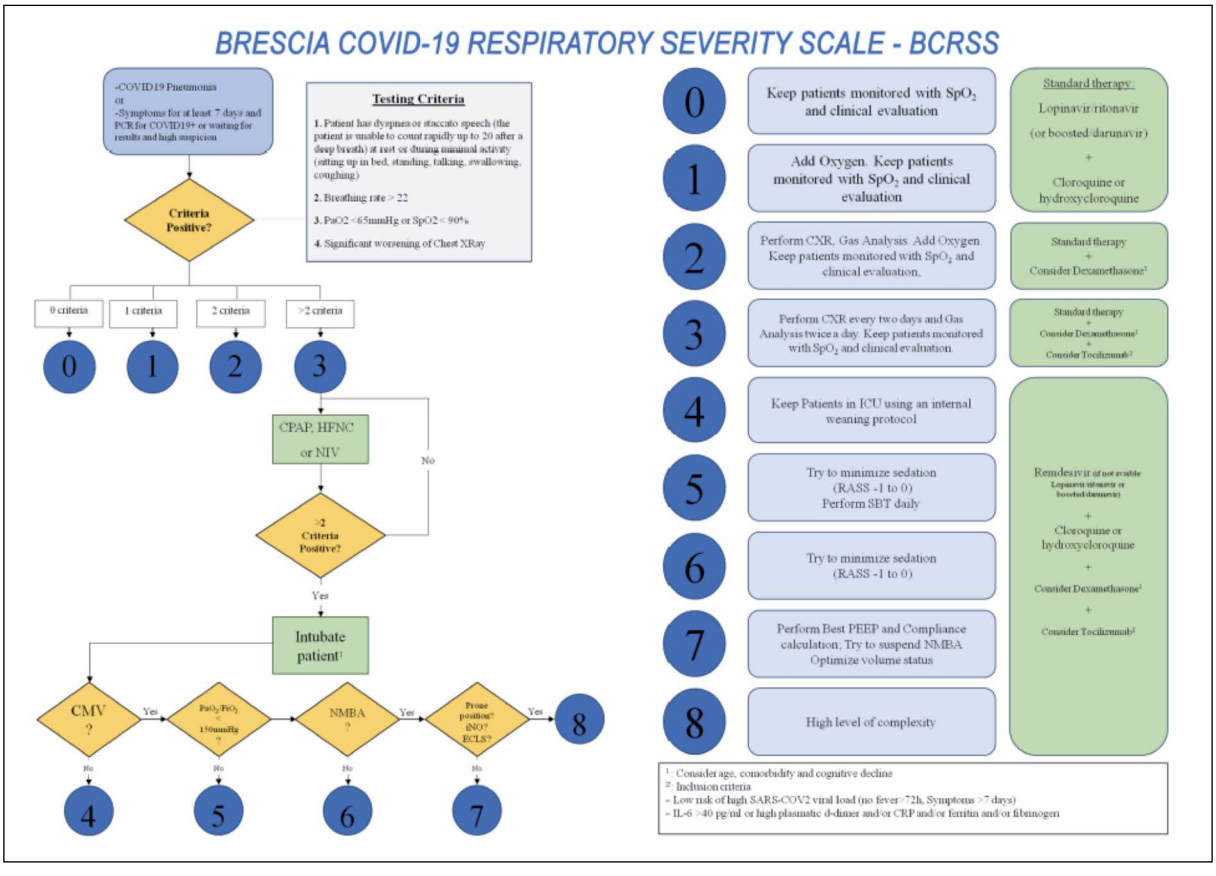
– with mild symptoms but with co-morbidities or increased risk of mortality (see above);
– with clinical manifestations of moderate or severe disease.

The Working Group is in favor of an early start of antiviral therapy. In case of delay in diagnosis due to the swab for COVID-19 turnover time, in presence of suggestive clinical picture (interstitial pneumonia) it is reasonable to start antiviral treatment as soon as possible even without the viral swab report (*e.g.*, in the emergency department).

Pharmacological treatment

Chloroquine

Clinical studies in vitro and in the animal models showed the antiviral activity of chloroquine phosphate against the SARS virus and avian flu



[8-10]. It seems indeed that chloroquine exerts its antiviral activity by increasing the endosomal pH interfering with the process of virus/cell fusion; moreover, chloroquine appears to impair the glycosylation of SARS COV 19 cell receptors. Chloroquine has also an immunomodulatory activity, which could amplify the antiviral activity *in vivo*. The drug has a good penetration in tissues even after oral administration of a 500 mg dose. 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 its use is associated with an improvement in the rate of clinical success, with a 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 [11]. Alternatively, if chloroquine is not available, hydroxychloroquine 200 mg BID can be used.
The Working Group recommends against the possibility of using chloroquine/hydroxychloroquine in prophylaxis for COVID-19. At present there is no evidence of efficacy of this drug in prophylaxis of COVID-19 disease; therefore, this strategy is not recommended.

Lopinavir/ritonavir (LPV/r)
Lopinavir (LPV) is a well-known second generation antiretroviral that inhibits the viral HIV protease. In combination with ritonavir (RTV) (an antiretroviral administered at low dosage, only as a lopinavir booster), it has significantly reduced morbidity and mortality in patients with HIV/AIDS. LPV/r is considered to be a promising treatment option for COVID-19 infections, based on its proven efficacy against SARS-COV (in combination with ribavirin) [12].
Although increasing in the last month, evidence of LPV/r clinical efficacy remains limited and mainly from anecdotal cases [13]. Similarly, anecdotal cases suggest that LPV/r administration can reduce COVID-19 viral load very quickly [14]. A randomized controlled trial (MIRACLE trial) is currently underway with the aim of assessing the therapeutic efficacy of LPV/r + IFNb in patients with MERS-CoV infection [15].

Darunavir/ritonavir and darunavir/cobicistat
Darunavir (DRV) boosted with ritonavir or cobicistat (COBI) is a third generation antiretroviral that inhibits the viral protease and it is recommended by International Guidelines for the treatment of HIV/AIDS.
In the treatment of HIV/AIDS, it has demonstrated greater efficacy and tolerability than lopinavir/ritonavir; however, the evidence that may suggest its use in COVID-19 is very limited. Nonetheless, considering that its mechanism of action is very similar to that of LPV/r, it is reasonable to assume that it may exhibit similar anti SARS-CoV-2 efficacy.
A growing shortage of lopinavir/ritonavir was observed in Italy due to the increase in prescriptions during the COVID-19 epidemic; therefore, the COVID-19 Working Group suggests the use of darunavir/ritonavir 800/100 mg OD or darunavir/cobicistat 800/150 mg OD as an alternative in case of shortage of lopinavir/ritonavir.

Remdesivir (GS-5734)
Remdesivir (RDV) is a nucleotide analogue that 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.
Remdesvir has been shown to be active in preclinical studies on SARS-CoV and MERS-CoV infections by interfering with the viral polymerase of coronaviruses [16]. In animal models infected with MERS coronavirus, remdesivir appears to have greater efficacy compared to treatment with lopinavir/ritonavir plus interferon beta 1/b. Recently, a North American study group demonstrated that the prophylactic use of LPV/r-IFNb reduced the viral load but had little impact on disease parameters in an experimental MERS infection model in mouse; in addition, LPV/r therapeutic use, while improving lung function, did not reduce the viral replication or the development of severe lung disease [17]. In the same study, prophylactic and therapeutic use of remdesivir was shown to be active both in reducing viral load and in improving lung function parameters [17]. Another study on a MERS-Cov infection model in macaque confirmed the prophylactic and therapeutic activity of RDV [18].
In an *in vitro* model of Vero cells infected with the nCoV-2019BetaCoV/Wuhan/WIV/04/2019 strain, both RDV and chloroquine have been shown to be able to block infection at low concentrations [19]. Two clinical trials to assess the efficacy of remdesivir use in COVID-19 are currently underway in China:

– for moderate COVID19 infections (NCT04252664 - A Phase 3 Randomized, Double-blind, Placebo controlled 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-nCoVRespiratory Disease).

TREATMENT PROTOCOL

COVID-19 positive patient
– Asymptomatic or with mild symptoms: (temperature >37.5°C, cough, respiratory symptoms without dyspnea);
– age <70 years;
– without risk factors (COPD, diabetes and heart disease);
– with negative chest X-ray.

Clinical monitoring, 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 (temperature >37.5°C, cough, dyspnea mild to moderate) and evidence of pneumonia on chest X-ray.

Lopinavir/ritonavir 200/50 mg, 2 tablets x 2/day (alternatively darunavir 800 mg 1 tablet/day + ritonavir 100 mg 1 tablet/day or darunavir/cobicistat 800/150 mg 1 tablet/day), + chloroquine 500 mg, 1 x 2/day or hydroxychloroquine tablets 200 mg, 1 x 2/day.
Duration of therapy: from 5 to 20 days, according to clinical response.

In case of oxygen therapy requirement or rapid clinical deterioration (see paragraph "support measures" and COVID respiratory severity scale) request remdesivir for compassionate use. When RDV available, stop LPV/RTV (or DRV/CBS and continue treatment with:
– remdesivir ampoules 150 mg: 200 mg loading dose, administered intravenously slowly-infusion over 30 minutes - on day one, then 100 mg iv/day from day 2 to day 10 (duration of treatment 10 days);
– in combination with chloroquine 500 mg, 1 x 2/day or hydroxychloroquine 200 mg, 1 x 2/day (duration of therapy: 5 to 20 days, according to clinical response).

In patients with BCRSS score equal or greater than 2 consider:
– dexamethasone 20 mg/day for 5 days then 10 mg/day for 5 days (indication must be discussed with intensive care team) and/or tocilizumab (see specific paragraph page 11).

COVID-19 positive patient
– With severe pneumonia, ARDS or overall respiratory failure;
– hemodynamic instability;
– need for mechanical (or non-invasive) ventilation.

Remdesivir ampoules 150 mg: 200 mg loading dose, administered intravenously slowly-infusion over 30 minutes - on day one, then 100 mg iv/day from day 2 to day 10 (duration of treatment 10 days)
+ chloroquine 500 mg x 2/day or hydroxychloroquine 200 mg x 2/day via nasogastric tube (NGT) (duration of therapy: 5 to 20 days, according to clinical response).

While waiting for remdesivir availability, start LPV/r oral solution (80/20 mg/mL) 5 mL x 2/day (or in alternative DRV/r oral suspension or DRV/c crushed and dispersed) via NGT + hydroxychloroquine 200 mg x 2 via NGT.

In patients with ARDS, 24 hours after ARDS diagnosis
Dexamethasone 20 mg/day for 5 days then 10 mg/day for 5 days (indication must be discussed with intensive care team) and/or tocilizumab (see specific paragraph).

DRUG INTERACTION AND DRUG SHORTAGE

The Group recommends careful consideration of drug to drug interactions, especially between LPV/r and other drug classes. In patients who are taking other medications, the Group recommends always checking for potential interactions on the website: http://www.covid19-druginteractions.org/
In patients in whom the use of LPV/r is contraindicated due to potential drug interactions, the

Group recommends using chloroquine/hydroxichloroquine alone.
The Group recommends using LPV/r tablet formulation and oral suspension only in patients with swallowing difficulties. LPV/r tablets cannot be crushed, therefore, if oral suspension of LPV/r is not available, oral suspension of darunavir (100 mg/ml, dose of 8 ml), in association with oral suspension of ritonavir (80 mg/mL, dose of 1.25 ml) can be used. In case of shortage of darunavir oral suspension, the Group reminds that both darunavir and darunavir/cobicistat co-formulation tablets can be crushed and administered via nasogastric tube (NGT) in dispersion [20].

Concomitant antimicrobial/antiviral treatment
The use of empirical or targeted antibiotic or antiviral treatment (oseltamivir) should be considered only in presence of a reasonable suspect of concomitant bacterial or viral infection.

Access to medications
Off-label use of registered drugs such as LPV/r and chloroquine/ hydroxychloroquine should follow off-label drugs use norms and local protocols.
Remdesivir is not yet a registered drug and therefore it requires a request to Gilead Sciences inc. for compassionate use on individual bases and needs approval of the local ethical committee.

Tocilizumab
Severe cases of COVID-19 infection are characterized by a severe pneumonia and rapidly evolving respiratory insufficiency, with elderly people and immunosuppressed persons at higher risk of developing severe disease and ARDS.
A recent study showed that patients requiring

Simplified treatment scheme.

Disease severity	*Clinical presentation*	*Support/antinflammatory treatment*	*Antiviral treatment*	*Notes*
Asymptomatic patient		None/surveillance	None	
Patient with mild respiratory symptoms, without additional risk factors	Fever (>37,5°C), cough, coryza. No dyspnea	Symptomatic therapy	None	
Patient with mild respiratory symptoms and age >70 years and/or comorbidities *Patient with moderate respiratory symptoms and/or pneumonia on CXR*	Fever (37.5°C), cough, mild to moderate dyspnea	Symptomatic Therapy, Oxygen therapy If BCRSS score >=2 Consider dexamethasone 20 mg/day for 5 days, then 10 mg/day for 5 days (upon discussion with intensive care team) and/or tocilizumab (see below)	*Preferred:* **lopinavir/ritonavir 400/100 mg BD + chloroquine** 500 mg BD or **hydroxychloroquine** 200 mg BD (5 to 20 days, duration depending on clinical response) *Alternative:* [***darunavir/ritonavir*** *(800/100 mg)*] or [***darunavir/cobicistat*** *(800/150 mg)*] + [***chloroquine*** *500 mg BD*] or [***hydroxychloroquine*** *200 mg BD*]	If clinical worsening and oxygen therapy needed, consider requesting **Remdesivir** (see patient with severe symptoms)
Critically ill patient	ARDS, haemodynamic instability, Multi Organ Failure (MOF)	Refer patient to ICU team and transfer to ICU 24 hours after ARDS diagnosis: dexamethasone 20 mg/day for 5 days, then 10 mg/day for 5 days (upon discussion with intensive care team) and/or tocilizumab	*Preferred:* **remdesivir** loading dose on the first day of 200 mg/ev followed by a maintenance dose of 100 mg/ev/day from day 2 to day 10 **+ [chloroquine]** or [hydroxychloroquine] (see above) ***Alternative*** *(or while waiting for remdesivir availability)*: (see above: patient with moderate symptoms/high risk)	

admission to ICU present with a cytokine storm with increased plasma concentrations of interleukins IL-6, IL-2, IL-7, and IL-10 and tumour necrosis factor TNF-α. A similar abnormal cytokine release pattern is observed in the cytokine release syndrome (CRS) associated with chimeric antigen receptor (CAR)-T cell therapy. CRS is characterized by fever and multiorgan failure. Cytokines involved in pathogenesis of CRS clinical manifestations are IL-6, interferon gamma (IFN-γ), TNF-α and IL-10 [21]. In particular, the central mediator of CRS toxicity is IL-6 [22].

Immunomodulant treatment is not routinely recommended in COVID-19 pneumonia. However, given the clinical and laboratory findings consistent with CRS and given the pathology reports of pulmonary oedema and hyaline membranes formation, it seems that a short duration targeted treatment could be beneficial in selected patients with severe pneumonia and/or ARDS, in association with respiratory support.

Tocilizumab is a monoclonal antibody which targets the IL-6 receptor. Intravenous administration is indicated in CSR associated with CAR-T treatment. Tocilizumab could be indicated for the treatment of COVID-19 in patients with severe and extensive lung disease with elevated IL-6 levels, in order to stop the systemic inflammatory response syndrome caused by the viral induced cytokine storm.

A clinical trial to evaluate the use of tocilizumab for the treatment of COVID-19 is currently underway in China, in the province of Anhui (ChiCTR 2000029765). In this trial, tocilizumab is given at a dose of 8 mg/kg, to be repeated after 12 hours.

In a pilot study in China (Effective Treatment of Severe COVID-19 Patients with tocilizumab, in press), Xiaoling Xu administered a single dose of tocilizumab 400 mg i.v.; a second dose could be administered in case of poor clinical response. The study showed promising results in 21 patients, who had a significant clinical improvement of lung function and fever, and a decrease of IL-6 level after treatment with tocilizumab.

In CRS, tocilizumab is administered slowly (infusion over 60 minutes) intravenously at a dose of 8 mg/kg in patients >30 kg or 12 mg/kg in patients <30 kg. In patients with poor response, two additional doses (maximum 3 doses in total) can be administered, with a minimum of 8 hours interval between doses.

Patient selection

The Lombardy COVID-19 Working Group recommends careful patients' selection for tocilizumab treatment.

The Working Group in collaboration with critical care teams proposes to use the Brescia-COVID respiratory severity scale (BCRSS) to select candidates to this treatment.

Inclusion criteria

- The high viral load phase of the infection is considered terminated (*e.g.*, apyretic for >72 h and/or at least 7 days after the onset of symptoms).
- Worsening respiratory insufficiency, requiring non-invasive ventilation or intubation (BCRSS score ≥3).
- High levels of inflammatory markers such as IL-6 (>40 pg/mL) (alternatively high levels of d-dimer (>1500 or rising), CRP, ferritin or fibrinogen).

Exclusion criteria

- Age <18 years AST/ALT more than 5 times above upper normal limit.
- Neutrophil <500 cells/mmc.
- PLT <50,000 cells/mmc.
- Documented sepsis from other pathogens, different from SARS-CoV-2.
- Presence of co-morbidities linked to an unfavorable outcome (clinical judgment).
- Complicated diverticulitis or bowel perforation.
- Skin/soft tissue infection (e.g., soft tissue infection not adequately controlled with antibiotic treatment).
- Immunosuppressive anti-rejection therapy.

Proposed protocol

A. Maximum 3 infusions each 8 mg/kg (maximum dose per infusion 800 mg).
B. Second infusion 8-12 hours after the first.
C. If partial or incomplete clinical response, potential third infusion 8-12 hours after the second infusion.

24 hours after 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 steroids (dexamethasone).

	Dosing Tocilizumab	*Range mg/kg*
35-45 kg	320 mg (4 x 80 mg vials)	9,1-7,1
46-55 kg	400 mg (1 x 400 mg vials)	8,7- 7,3
56-65 kg	480 mg (1 x 400 mg vial + (1 x 80) mg vial)	8,6-7,4
66-75 kg	560 mg (1 x 400 mg vial + 2 x 80 mg vial)	8,5-7,5
76-85 kg	600 mg (1 x 400 mg vial + 1 x 200 mg vial)	7,9-7,0
>86 kg	800 mg (2 x 400 mg vial)	9,3

Drug availability
While tocilizumab is registered in Italy, its use in COVID-19 infection is off-label; therefore appropriate local procedures for the use of off-label drugs should be followed. Informed consent should be given by the patient, unless in emergency context and in the patient's best interest.

Adverse effects
Please refer to formulary for adverse effects that are not specified in this document.

Pregnancy
Tocilizumab is a monoclonal antibody and is not teratogen. Placental transfer can be expected from the 16th gestational week, in analogy with all IgG. Therefore, the concentration of the drug could be higher in fetal blood compared to the mother's blood towards the end of pregnancy.
Therefore, the Group recommends careful consideration of risks and benefits of treatment, bearing in mind that it is possible that newborns that have been exposed in utero during the third trimester of pregnancy can be temporarily immunosuppressed, for the time required to clear the drug absorbed from the mother.

Supportive antimicrobial/antiviral treatment and latent infections reactivation
The Group recommends a careful evaluation for the presence of concomitant infections and considering the initiation of a broad spectrum preventive antibiotic treatment according to clinical indications, local protocols and antimicrobial guidelines.
The Group recommends screening for latent tuberculosis with IGRA tests and for latent HBV infection with viral markers. However, given the urgency of treatment initiation, the Group suggests that treatment can be initiated while waiting for the results of the screening tests.

Conflict of interest
None.

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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*. Retrieved from http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51. Last accessed February 20, 2020.
[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; 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, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomized controlled trial. *Lancet Respir Med*. 2020; 8 (3), 267-76.
[8] 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.

[9] Vincent MJ, Bergeron E, Benjannet S, et al. Virol. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005; 2, 69.
[10] Yan Y, Zou Z, Sun Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. *Cell Res*. 2013; 23(2), 300-2.
[11] 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; 43, E019.
[12] Chu CM, Cheng VC, Hung IF, et al. HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004; 59 (3), 252-6.
[13] Han W, Quan B, Guo Y, et al. The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019. *J Med Virol*. 2019; 92 (5), 461-3.
[14] Lim J, Jeon S, Shin HY, 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; 35 (6), e79.
[15] Arabi YM, Asiri AY, Assiri AM, et al. and the Saudi Critical Care Trials group Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. *Trials*. 2020; 21 (1), 8.
[16] Agostini ML, Andres EL, Sims AC, 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.
[17] Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun*. 2020; 11, 222.
[18] de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci USA*. 2020; pii: 201922083.
[19] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2019; 30 (3), 269-71.
[20] Brown K, Thomas D, McKenney K, et al. Impact of Splitting or Crushing on the Relative Bioavailability of the Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet. *Clin Pharmacol Drug Dev*. 2019; 8 (4), 541-8.
[21] Wang Z, Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. *Biomark Res*. 2018; 6, 4. doi: 10.1186/s40364-018-0116-0. eCollection 2018.
[22] Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014; 124 (2), 188-95. doi: 10.1182/blood-2014-05-552729. Epub 2014 May 29. Erratum in: *Blood*. 2015; 126 (8), 1048. Dosage error in article text. *Blood*. 2016; 128 (11), 1533.