



Clinical Management of Adult Coronavirus Infection Disease 2019 (COVID-19) Positive in the Setting of Low and Medium Intensity of Care: a Short Practical Review

Alfredo Pennica¹ · Giulia Conforti² · Francesca Falangone² · Antonio Martocchia² · Laura Tafaro² · Alberto Sentimentale² · Valentina Marini² · Aldo Pezzuto² · Valerio Spuntarelli² · Paolo Martelletti²

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Abstract

Coronavirus disease 2019 (COVID-2019) is a viral infection which is rapidly spreading on a global scale and causing a severe acute respiratory syndrome that affects today about four and a half million registered cases of people around the world. The aim of this narrative review is to provide an urgent guidance for the doctors who take care of these patients. Recommendations contained in this protocol are based on limited, non-definitive, evidence and experience-based opinions about patients with low and medium intensity of care. A short guidance on the management of COVID-19 is provided for an extensive use in different hospital settings. The evidence-based knowledge of COVID-19 is rapidly evolving, and we hope that, in the near future, a definitive and most efficacious treatment will be available including a specific vaccine for SARS-CoV-2.

Keywords COVID-19 · Low-medium intensity of care · Therapy · Management

Introduction

Coronavirus disease 2019 (CoViD-19) is a rapidly spreading viral infection causing a severe acute respiratory syndrome that affects today about four and half million people globally [1]. Given the rapid pace of scientific discovery and clinical data generated by the large number of people rapidly infected by SARS-CoV-2, we aim to provide in this narrative review an evidence and experience-based guidance for clinicians involved in the care of COVID-19-positive adults in a setting of low/medium intensity of care.

Classification and Risk Stratification for Management of COVID-19

As the WHO stated, a confirmed COVID-19 case is defined as “a case with laboratory confirmation for SARS-CoV-2 infection carried out at the reference laboratory, regardless of the clinical signs and symptoms presented” [2].

The clinical presentation is heterogeneous: about 80% of confirmed cases are considered “mild”, involving mostly cold-like symptoms to mild pneumonia; 15% are “severe”, involving serious pneumonia and shortness of breath; the remaining 5% develop respiratory failure, septic shock, and/or multi-organ failure—“critical cases”—potentially resulting in death [3]. The second week appears to be the most dangerous for a potential clinical worsening, according to the data [4]. Cases of asymptomatic infection are also possible, but their frequency is not known at present [5].

In accord to the WHO definitions [2], we may have the following:

- Uncomplicated disease: limited to upper respiratory tract viral infection; nonspecific symptoms such as fever, malaise, cough, pharyngodynia, nasal congestion, headache, or muscle pain. On rare occasion, patients may also

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✉ Paolo Martelletti
paolo.martelletti@uniroma1.it

¹ Infectious Disease Unit, Sant’Andrea Hospital, Sapienza University, Rome, Italy

² Emergency Medicine CoViD-19 Unit, Sant’Andrea Hospital, Sapienza University, Rome, Italy

present with diarrhea, nausea, and vomiting. No signs of severe pneumonia. Adolescent or adult immunosuppressed may exhibit atypical symptoms.

- Mild pneumonia: clinical and/or radiological diagnosis of pneumonia but no signs of severe pneumonia and no need for supplemental oxygen (SpO₂ > 90% in air). The diagnosis is clinical, and chest imaging is helpful to rule out complications.
- Severe pneumonia that includes fever or suspected respiratory infection, plus any of the following conditions:

- Respiratory rate > 30 acts/min
- Dyspnea
- SpO₂ < 90% in air

- ARDS (acute respiratory distress syndrome) (definition of Berlin 2012) [6]:

- New onset or worsening respiratory symptoms, within a week of exposure to the causative agent
- Imaging (radiography, CT, pulmonary ultrasound): bilateral opacities not related to cardiogenic edema, effusions, atelectasis, and pulmonary nodules
- Cause of edema not referable to heart failure or fluid overload. Accurate instrumental evaluation (e.g., echocardiography) is necessary to exclude cardiogenic pulmonary edema in the absence of risk factors [6]
- Oxygenation (adults):

Mild ARDS, 201 mmHg < P/F ≤ 300 mmHg

Moderate ARDS, 101 mmHg < P/F ≤ 200 mmHg

Severe ARDS, P/F ≤ 100 mmHg

To evaluate the severity of COVID and to determine the correct management, we may refer to slightly different scales [7, 8], and we refer to the Modified Early Warning Score (MEWS), an exclusively clinical evaluation system [8].

The MEWS is a rapid and simple application tool, which provides a useful aid in deciding on the correct allocation of the patient, based on the intensity of monitoring and treatment required (see Table 1). Using MEWS score, we may have the following: stable patient (score 0–2), instable patient (score 3–4), and critical conditions (score ≥ 5).

Another tool being used in Italy, though not externally validated, is the Brescia-COVID Respiratory Severity Scale (BCRS) (Table 2) [9]. This is a stepwise approach to managing patients with confirmed/presumed COVID-19 pneumonia. On the basis of four clinical-instrumental criteria, the patient is assigned to one of eight levels of care.

Levels 0–3 are managed in a non-critical area, while levels from 4 to 8, inclusive, require intensive care (<https://cdn-webimg.mdcalc.com/content/BRSS>).

In our low-medium intensity care unit, we manage cases of mild/severe COVID-19 pneumonia (MEWS 0–3; BCRS 1–3) that require medical support therapy, oxygen therapy, frequent monitoring of vital parameters and oxygenation with pulse oximetry, and arterial gas analysis. Continuous clinical reassessment is essential because of the high risk of sudden deterioration.

Therapeutic Approach

At present, there are no antiviral drugs registered for use in patients with COVID-19. Supportive care [10–12] is standard of care, and the currently available drugs are as follows:

- Protease inhibitors (lopinavir/ritonavir; darunavir + ritonavir; darunavir/cobicistat) [10], already used for the chronic treatment of HIV infection and promising treatment option for COVID-19 infections, based on the proven efficacy against SARS-CoV (in combination with ribavirin) [13]. Clinical evidence however remains limited. The effectiveness of lopinavir/ritonavir is suggested by anecdotal cases [14]. In a similar way, anecdotal cases suggest how this administration is able to reduce the viral load of COVID-19 very quickly [15]. Three randomized, open-label clinical trials are currently listed on <https://clinicaltrials.gov/> evaluating darunavir/cobicistat as a potential therapeutic option for COVID-19.
- Chloroquine or hydroxychloroquine, drugs used in malaria, amebiasis, and in some diseases with autoimmune pathogenesis; clinical studies have shown the activity in vitro and in the animal model of chloroquine phosphate as an antiviral against the SARS virus [16, 17] and avian influenza [18]. Despite the lack of clear evidence of benefit, hydroxychloroquine is recommended off label for the treatment of COVID-19 by the Chinese National guidelines [19, 20], and the US Food and Drug Administration has issued an Emergency Use Authorization for the treatment of adult patient with COVID-19. By contrast, the IDSA (Infectious Disease Society of America) recently concluded that because of insufficient data, they could not recommend any particular treatment for patients with COVID-19 [21].
- Azithromycin, an antibiotic belonging to the macrolide family [22].
- Tocilizumab, monoclonal antibody, already used in the treatment of severe syndromes caused by release of cytokines induced by CAR-T lymphocytes (chimeric antigen receptor T cell) [23].
- Remdesivir (GS-5734) is a broad-spectrum antiviral nucleotide with potent in vitro activity against a range of RNA viruses including Ebola virus, Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus, Nipah

Table 1 MEWS score [8]

MEWS score	3	2	1	0	1	2	3
Heart rate		< 40	40–50	51–100	101–110	111–130	> 130
Systolic BP (mmHg)	< 70	70–80	81–100	101–200		> 200	
Respiratory rate		< 9		9–14	15–20	21–30	> 30
Temperature (°C)		< 35.1	35.1–36.5	36.6–37.5	> 37.5		
AVPU score				A (alert)	V (response to voice)	P (reacting to pain)	U (unresponsive)

BP blood pressure. AVPU score Alert-Voice-Pain-Unresponsive score

Worried about patient’s condition, 1 point

Urine production below 75 cc during previous 4 h, 1 point

Saturation below 90% despite adequate oxygen therapy, 3 points

virus, and Hendra virus [24–26]. The mechanism of action of remdesivir is premature termination of viral RNA transcription.

- Methylprednisolone 20 mg × 2/day, according to clinical/radiological judgment and the presence of any of these conditions:

- Hypoxia at rest in ambient air (SpO2 < 93%, pO2 < 70 mmHg)
- Respiratory rate > 30 acts/min in ambient air
- P/F ratio ≤ 300 mmHg
- CT scan with severe, extensive, bilateral interstitial involvement with fibrotic evolution

- Sodic Enoxaparin [27]:

- Low-intensity care COVID-19 wards: 100 U/Kg/day; 70 U/Kg × 2/day for obese patient (BMI > 30) or at particularly high thrombotic risk (e.g., neoplasms, previous DVT)

- Intermediate/high-intensity care COVID-19 departments: 70 U/Kg × 2/day

- Antibiotic therapy: we suggest to use only in cases in which a superinfection cannot be excluded. For community-acquired forms of bacterial pneumonia (CAP), a third-generation cephalosporin, clarithromycin, or azithromycin or alternatively fluoroquinolones can be inserted, with attention to these last two due to the effect of elongation on QT.

In a low/intermediate care setting, such as the one in which we are working and to which this review is directed, we propose two possible therapeutic schemes, extrapolated from clinical experience and scientific evidence currently available but nevertheless continuously evolving, accelerated by the ongoing emergency. The schemes suggested are:

- Scheme A Hydroxychloroquine 200 mg × 2/day or 3/day (or chloroquine 500 mg × 2 day) [20] + lopinavir/ritonavir

Table 2 Brescia-COVID Respiratory Severity Scale (BCRS) [9]

Criteria score	Testing criteria
0	Patient has dyspnea or staccato speech (the patient is unable to count rapidly up to 20 after a deep breath) at rest or during minimal activity (sitting up in bed, standing, talking, swallowing, coughing)
1	Breathing rate > 22
2	PaO2 < 65 mmHg or SpO2 < 90%
> 2 but no NIV, HFNC, or CPAP	Significant worsening of chest X-ray
> 2 and NIV, HFNC, or CPAP	Keep patients monitored with SpO2 and clinical evaluation
	Add oxygen, keep patients monitored with SpO2 and clinical evaluation
	Keep patients monitored with SpO2 and clinical evaluation, perform chest X-ray, gas analysis
	Keep patients monitored with SpO2 and clinical evaluation, perform chest X-ray every 2 days, gas analysis twice a day
	Keep patients in ICU

NIV noninvasive ventilation, HFNC high flow nasal cannula, CPAP continuous positive airway pressure, ICU intensive care unit

200/50 mg \times 2/day (or darunavir/cobicistat 800/150 mg day or darunavir 800 mg day + ritonavir 100 mg day)

- Scheme B Hydroxychloroquine 200 mg \times 2/day or 3/day (or chloroquine 500 mg \times 2 day) [20] + azithromycin 500 mg day.

In Scheme A, in our unit, we prefer the use of darunavir + ritonavir or darunavir/cobicistat, although with less scientific evidence than lopinavir/ritonavir, because of its greater tolerability.

Scheme B seems to be supported by the recent publication of Gautret et al. that shows how hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients, effect reinforced by azithromycin [22]. However, the latest NIH COVID-19 guidelines panel and IDSA guideline panel recommend against this combination, except in the context of a clinical trial, for adverse effects, especially prolonged QTc interval [28, 21].

We consider the addition of heparin to these schemes if no contraindications are present.

Therapy should be continued for 7–20 days with timing to be established according to clinical evolution.

All these drugs have to be seriously evaluated for interactions with other therapy (in particular using lopinavir/ritonavir) and for the adverse events:

- Hydroxychloroquine and chloroquine can lengthen the QTc for which they need periodic ECG assessment and can lead to lesions of the retina and to glycidic intolerance.
- Azithromycin can also lengthen the QTc, which requires periodic ECG assessment.
- Lopinavir/ritonavir can cause diarrhea, nausea, vomiting, and increased amylase and lipase.
- Darunavir/cobicistat may give rise to creatinine, amylase, and lipase.
- Darunavir + ritonavir can increase amylase and lipase.

For the management of these drugs in relation to adverse effects on QTc interval, we refer to SIC guidelines (<https://www.sicardiologia.it/public/SIC-Covid-e-QT.pdf>), while for the possible interactions with other drugs, we consult <http://www.covid19-druginteractions.org/>.

Up to 20% of mild/moderate infections can develop into ARDS [2]. If rapid clinical deterioration during standard therapy occurs and oxygen therapy is needed, remdesivir can be used for compassionate use [29]. As soon as available, suspend Scheme A or B and continue with remdesivir 200 mg on day 1 then 100 mg/day for another 9 days in combination with chloroquine 500 mg, 1 \times 2/day or hydroxychloroquine 200 mg, 1 \times 2/day. If the patient develops a BCRSS score 3 or MEWS \geq 3, evaluate dexamethasone and/or tocilizumab.

Tocilizumab should be administered in apiretic patient $>$ 72 h and/or at least 7 days after the onset of symptoms, if there is a worsening of gas exchange (BCRSS score \geq 3) and if there are high levels of IL6 (or D-dimer and/or RCP and/or ferritin and/or fibrinogen increasing progressively). Patients aged $<$ 18 years or with one or more of these conditions, transaminases greater than 5 times the norm, neutrophil value $<$ 500 cell/mmc, PLT $<$ 50,000 cells/mmc, sepsis, comorbidities related to an unfavorable outcome, diverticulitis or intestinal perforation, ongoing skin infection, and immunosuppressive antirejection therapy, should be excluded for tocilizumab therapy.

The therapeutic scheme recommended is for a maximum of 3 infusions at a dosage of 8 mg/kg body weight (maximum dosage per infusion 800 mg) with the second infusion done 8–12 h after the first. If clinical response is partial or incomplete, a third infusion 16–24 h after the first infusion is possible. After 24 h 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) [30].

Type and Timing COVID-19 Positive Patient Assessment

In our low/medium intensity ward, we have drawn up a protocol of patient's examinations to be requested both at the time of admission and during the course of the hospital stay, based from evidence and clinical judgment.

We present in details in Table 3.

Transfer and Discharge Criteria

COVID patients are in a delicate equilibrium, so they must be constantly monitored owing to the sudden high risk of clinical deterioration, especially during the second week of illness [2]. A patient who develops dyspnea, tachypnea ($>$ 30 acts/min) with desaturation (SpO₂ $<$ 90%), and changes MEWS score in level 3–4 may require to be transferred to a subintensive critical area for the management of acute respiratory insufficiency and for noninvasive mechanical ventilation.

The appearance of respiratory distress, severe respiratory failure, diagnosis of ARDS, cardiovascular shock and multi-organ failure (MOF), severe agitation, severe sensory alteration, a state of epileptic illness, and serious arrhythmias potentially at risk of cardiovascular arrest led to a clinical reassessment with a MEWS score $>$ 4, and the patient should be promptly transferred to an intensive care unit (ICU).

Table 3 Type and timing of COVID-19 positive patient assessment

Assessment		Monitoring	
Clinical	Blood pressure	Every day	
	Heart rate	Every day	
	Breath frequency	Every day	
	Pulse oximetry	Every day	
Laboratory	Complete blood count	All at baseline and discharge	
	Lymphocyte subpopulation		
	Serum electrolytes (Na, K, Mg, Ca)	Complete blood count, Na, K, Ca,	
	Renal function		
	Hepatic function	Creatinine, hepatic function, pancreatic function, D-dimer, RCP, ferritin every 2 days	
	Pancreatic function		
	Coagulation (PT, PTT, D-dimer, fibrinogen)	RCP, ESR, ferritin	
	LDH		
	Blood gas analysis, at baseline and repeat if sat < 95%	At least 2 samples of blood cultures every febrile peak	
	Urinary pneumococcal and Legionella antigens		
	Instrumental	Chest X-ray	Once a week
		Chest CT	At baseline and after 10 days of therapy
		ECG, keep K ⁺ between 4 and 5 mmol/L	Every 3–4 days if QTc < 460 msec Every 2 days if QTc 460–500 msec Continuous if QTc 500–550 msec Stop therapy if QTc > 550 msec

If the clinical course, on the other hand, is favorable and the patient meets both a clinical and laboratory improvement, two pathways open the following:

- Discharge at home when buffer is negative (at least two negative tests collected 24 h apart) and any symptoms of SARS-CoV-2 infection have disappeared.
- Discharge in care structures when buffer is positive but the patient is stably afebrile, the respiratory rate < 22 respiratory acts per minute and the oxygen saturation is > 95%.

Conclusion

Coronavirus disease 2019 (COVID-2019) is a rapidly spreading viral infection causing a severe acute respiratory syndrome that affects today about four and a half million people around the world. The purpose of this narrative review is to provide an urgent guidance for doctors taking care of patients in low/medium intensity care settings. We have tried to give management suggestions based on our experience and based on data collected from

the international scientific evidence currently available but which is nonetheless continuously evolving, accelerated by the ongoing emergency. First of all, the patient's stratification risk is to be established with severity score now available (MEWS or BCRSS); as soon as patients are hospitalized in non-intensivist wards, it is necessary to act with supportive therapeutic schemes, offer continuous clinical surveillance and be ready to recognize, and direct the patients who deteriorate into the sub-intensive and intensive areas. Secondly, we have to be able to identify the recovered patient and/or clinically healed, discharge, and give all the advice for keeping them and their relatives in safety.

In addition to our recommendations, we ask that the providers who care for the COVID-19 patients follow the specific policy in place by their institutions, hospitals, states, or federal governments to ensure that the patients' management are in line with our guidance.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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