



SARS-CoV-2: recommendations for treatment in intensive care medicine

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Summary Coronavirus disease 2019 (COVID-19) progresses mildly in most of the cases; however, about 5% of the patients develop a severe acute respiratory distress syndrome (ARDS). Of all COVID-19 patients 3% need intensive care treatment, which becomes a great challenge for anesthesiology and intensive care medicine, medically, hygienically and for technical safety requirements. For these reasons, only experienced medical and nursing staff in the smallest grouping possible should be assigned. For these team members, a consistent use of personal protective equipment (PPE) is essential.

Due to the immense medical challenges, the following treatment guidelines were developed by the ÖGARI (Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin), FASIM (Federation of Austrian Societies of Intensive Care Medicine) and ÖGIAIN (Österreichische Gesellschaft

für Internistische und Allgemeine Intensivmedizin und Notfallmedizin).

The recommendations given in this article are to be understood as short snapshots of the moment; all basic guidelines are works in progress and will be regularly updated as evidence levels, new study results and additional experience are gathered.

Keywords SARS-CoV-2 · COVID-19 · ARDS · Personal protective equipment · Respiratory therapy

Introduction

The recommended procedures for the prognosis, admission, diagnosis and treatment management described in this paper are based on the “ICU Therapy Guidelines for the Treatment of Patients with a SARS

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CoV 2 Infection”, compiled and published by the Austrian Society for Anesthesiology, Reanimation and Intensive Medicine (ÖGARI) and updated in an interdisciplinary paper together with the Federation of Austrian Societies of Intensive Care Medicine (FASIM) and the Austrian Society for Internal and General Intensive Medicine and Emergency Medicine (ÖGIAM) [1]. Reference is also made to the guidelines of the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM), “Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)” [2].

The professional societies who have published this information point out specifically that all of their recommendations concern this particular moment of time. Practically every day new publications change the level of information. Such a flood of information can easily lead to insecurity. International and national recommendations for treatment should be considered a work in progress. They are being constantly revised and adapted to the current evidence.

SARS-CoV-2

The virus SARS-CoV-2 causes the illness coronavirus disease 2019 (COVID-19). The median age of patients testing positive for SARS-CoV-2 is 44.5 years and 60% are male [3]. The illness in most cases runs a light course (mild pneumonia and slight breathing difficulties) [4]. Only a small proportion of those showing severe symptoms (about 5% of all COVID-19 patients) are admitted to hospital or treated in the ICUs [5]. In contrast to other infectious illnesses, the severe course of the illness from initial symptoms to life-threatening deterioration is a slow progression.

The transmission is primarily via droplet infection, above all coughing or sneezing but medical procedures, such as suctioning or intubation can transmit SARS-CoV-2. Theoretically, a smear infection via contaminated surfaces or excrement or eye conjunctiva is also possible. The incubation time is 5–6 days (median time 5.7 days), the span is from 1 to 14 days [6] and 97.5% of all cases become symptomatic after an interval of an average of 11.5 days [3, 7].

Patients with COVID-19 treated in ICU have a current mortality rate of 30–70% according to recent data [8]. This is not an especially high value for older patients with severe acute dyspnea syndrome (ARDS—acute respiratory distress syndrome). Survivors suffer from the usual effects of a long treatment in intensive care. Reports also show that subsequently there are accumulated cases of pulmonary fibrosis. While the evidence for this is weak, the possibilities should be considered in the post-illness monitoring.

Symptoms

The most common symptoms (Table 1) observed in COVID-19 patients are fever and a usually dry cough [9]. Further possible symptoms are headache and joint pain, additionally colds and sore throats, loss of appetite, weight loss, gastrointestinal syndromes, such as diarrhea, nausea, abdominal pain or vomiting, conjunctivitis, skin rashes, swollen lymph nodes, anosmia, apathy, sensory loss and more rarely respiratory distress [10].

In China, which issues the largest part of empirical data, about 80% of all known cases have the above-mentioned symptoms. About every fifth patient develops severe pneumonia with breathing problems, tachypnea, and/or gas exchange distress in the course of the illness [11]. Patients needing intensive care (about 3% of the cases) show key symptom dyspnea and 33% of these show bilateral shading in lung x-rays [12].

Admission

COVID-19 patients must be isolated immediately upon arrival at the hospital and the health authorities must also be informed.

Table 1 Diagnostic examinations in the intensive care unit (ICU)

Initial examination
<i>Swab of the upper respiratory tract: nose and throat swabs; deep respiratory tract: sputum, tracheal secretion or mini-BAL sample taking catheter (CAVE: strict indication positioning for bronchoscopy + BAL—only for further exact diagnosis of a superinfection!)</i>
<i>Intensive laboratory examinations</i>
<i>Blood gas analysis (BGA)</i>
2 blood cultures from 2 different areas
Differential diagnosis: influenza swab, RSV, Legionella or Pneumococcus Antigens, antigens in urine
Thorax x-ray on admission (if need be after inserting a CVC, stomach tube or after intubation)
Regular use of sonogram for progression diagnostics (B-lines)!
<i>CT thorax: routine CTs are advised against but recommended for specific issues</i>
Further examinations in the course of the illness
<i>Laboratory (blood count, albumin, creatinine, urea, bilirubin, LDH, CRP)</i>
Laboratory every 3 days, additionally myoglobin, IL-6, CK, CK-MB, troponin
Blood gas analysis
<i>Sonogram of lungs (pulmonary sonogram?)</i>
<i>Echo cardiogram, if needed</i>
In case of an increase in PCT (CAVE: superinfection)
<i>Blood cultures; urine cultures</i>
<i>if needed, sputum, or in intubated patients take tracheal secretions</i>
Further examinations for extrathoracic complications
<i>RSV Respiratory syncytial virus, CVC central venous catheter, CT computed tomography, LDH lactate dehydrogenase, CRP C-reactive protein, IL-6 Interleukin 6, CK Creatine kinase, CK-MB creatine kinase myocardial band</i>

Before entering the room, hospital staff have to put on personal protective equipment (PPE) according to the current standard of hygiene. These include, according to the latest recommendation of the Austrian Agency for Health and Nutritional Security (AGES), the following measures: hand disinfectant, protective gowns, gloves, head covering (surgical cap), protective glasses, masks (FFP2 or FFP3). Additional and continually updated information for hygienic guidelines can be found under: <https://www.sozialministerium.at/Themen/Gesundheit/Antimikrobielle-Resistenzen-und-Gesundheitssystem-assozierte-Infektionen/Gesundheitssystem-assozierte-Infektionen/Krankenhaushygiene-und-PROHYG/Krankenhaushygiene-Informationen-zu-nCov.html>

On leaving the room, the PPE is to be disposed of under consideration of a possible contamination.

There is a basic difference in necessary hygienic measures between normal exposure (for example, visitation in patients' rooms) and activities with aerosol production (e.g. swabbing, intubation, endotracheal suction with open suction systems, disconnecting equipment, tracheotomies, NIPPV [noninvasive positive-pressure ventilation] and HFNC [high flow nasal cannula]). For these activities, the University Clinic for Hospital Hygiene and Infection Control of the Medical University of Vienna defines its own hygiene guidelines: besides a close-fitting FFP3 mask (recommended by the European Center for Disease Prevention and Control, ECDC and the Robert Koch Institute, RKI) or a FFP2 mask (WHO [World Health Organization], Federal Health Agency BAG [Bundesamt für Gesundheit]), a long-sleeve gown, hood with neck protection, disposable gloves, protective glasses and visor that must be disinfected immediately after use and with expected contamination with fluids, a one-way apron should be worn. A detailed list of hygienic measures can be found under: https://www.meduniwien.ac.at/orgs/fileadmin/krankenhaushygiene/HygMappe/Richtlinien/101_Novel_Coronavirus_nCoV_vs12.pdf

The common guidelines of ÖGARI, FASIM and ÖGIAIN further recommend that contact with the patients in intensive care be reduced to the absolutely necessary measures for good medical and nursing care, that experienced teams remain small, and the highest measures of self-protection be observed. The same goes for all patient transport.

Diagnosics

The guidelines define procedures for initial and further examinations in progression. For patients in obligatory intensive care with unclear pneumonia, the usual suspects like influenza, pneumococcus, legionella should be tested for and if possible, tracheal secretion taken for microbiological analysis. In addition, two blood samples from different areas should be taken, if possible at the same time. In

case of suspicion of SARS-CoV-2, a nasopharyngeal/oropharyngeal swab should be submitted for testing. Specimen of lower respiratory tract (e.g. sputum) may have higher sensitivity. If the first finding is questionable and there is a high clinical suspicion with intubated patients, a bronchoalveolar lavage (mini-BAL) should be done for extracting secretion from the deep respiratory tract under the highest protective measures for the examiner. A case series also showed that the presence of glassy infiltrates in the thorax CT can also indicate a COVID-19 infection (<https://www.drg.de/de-DE/5995/covid-19/>) [13].

About 80% of SARS-CoV-2 positive patients show a lymphopenia in laboratory diagnostics; about 40% show thrombocytopenia, and increases in LDH and D-dimer cells, and about one third show leukopenia [14]. A massive lymphopenia, high CRP and high LDH values indicate a complicated, severe course of the illness, increased procalcitonin indicates a possible bacterial superinfection.

Treatment of hypoxia

According to reports, hypoxia is a dominant presentation in the pneumonia caused by SARS-CoV-2. The treatment protocol is based on the treatment guidelines for ARDS [15]. The goal of respiratory therapy is to re-establish an adequate oxygenation (SaO₂ value ≥92%; in patients with COPD ≥88%) and a clinically relevant improvement of respiratory distress and tachypnea (breathing frequency <30/min). The decision on the method of respiratory support or type of respiration depends among other things on the severity of the illness or the physiological response of the patient to the therapy.

In the case of a diagnosed moderate gas exchange disturbance, a supportive O₂ therapy should be initiated if SaO₂ values are 90% (however should be done with SaO₂ values ≤92%, in patients with pre-existing COPD ≤88%). In cases of acute hypoxia respiratory failure, SaO₂ values should not be increased above 96%.

If the O₂ therapy has insufficient efficacy, a high-flow nasal cannula (HFNC) is indicated. The flow should not be set higher than 10–20 L /min, in order to avoid additional danger for the staff through increased aerosol spread. An additional face mask with reservoir bag should be used for protection against aerosol droplets. If no HFNC is available, a non-invasive intermittent positive pressure ventilation (NIPPV) can alternatively be put over the mask or helmet. If no stabilization is achieved within an hour using HFNC or NIPPV, an early decision for endotracheal intubation should be made, because a delayed intubation is associated with a very poor outcome.

When using noninvasive forms of respiration, the self-protection of the staff is of especially high importance. HME (heat and moisture exchanger) filters

must be used unconditionally on each mask and other interfaces (as for example respiratory bags).

Intubation and mechanical ventilation

The success rate of noninvasive forms of respiration in critically ill COVID-19 patients is limited. For patients with severe hypoxia and/or clinically progressive respiratory failure, intubation and mechanical respiration with adequate PEEP values are the only possibilities to stabilize lung function.

Intubation is also a procedure with a very high risk of infection for hospital staff and so must be done under the strictest of personal safety measures and

with exact preparation and consultation. The use of a video laryngoscopy is recommended. A compact presentation of the safety measures can be seen in the picture airway management COVID-10 (Table 2).

A closed suction system should always be used with artificial respiration. With every tube disconnection, the tube should be pinched off first with a wide clamp.

The tidal volume is to be limited to 4–6(–8)ml per kg body weight. Plateau pressure over 30 cm H₂O is to be avoided. With progression of the lung pathology, especially if atelectasis occurs in independent lung areas, a regular change between supine and prone patient positions and a PEEP adjustment to prevent the formation of new atelectasis is necessary. Measures to minimize transpulmonary pressure should be used methodically, for example measuring esophageal pressure. Early use of the prone position (with Horovitz index ≤ 200) is recommended, whereby the duration of the form of therapy should be about 16h.

The implementation of a neuromuscular blockade can be considered in individual cases with synchronization problems with respiration. As rescue therapies, inhalation pulmonary vasodilation as well as the use of inhalation NO can be considered. A moderate hypercapnia (pCO₂ < 60 mmHg) is tolerable with advanced ARDS. Other rescue therapies can be considered, such as a venovenous extracorporeal membrane oxygenation (VV-ECMO). In this case, it is absolutely essential to contact a specialized center.

With the use of transport respirators with one-tube technology, patients must be transported with 100% oxygen. In case of low FiO₂ concentrations, the machines mix the oxygen with the room air around it, so that virus-contaminated air can get into the machine.



Hemodynamic management

A restrictive fluid intake therapy is recommended [19]. Noradrenalin should be used as the vasopressor of first choice. With insufficient success, adding vasopressin is recommended. The goal is a mean arterial pressure (MAP) of 60–65 mmHg; in the likelihood of hypertension, however, a higher MAP (75–80 mmHg) should be considered.

With unstable patients, additional hemodynamic monitoring, echo cardiogram, invasive hemodynamic monitoring, is recommended. In the case of a clear hemodynamic instability, hydrocortisone can be administered.

There are case reports about myocardial involvement in COVID-19 patients. Severe myocardial problems are still the exception. According to current information, the myocarditis occurring with SARS-CoV-2 infections is to be treated like any other viral myocarditis. Even with SARS-CoV-2-induced sepsis, the hemodynamic therapy progresses along the usual algorithms.

Table 2 Airway management COVID-19

Treatment recommendations for intubated (endotracheal) patients with confirmed infection or high-grade suspicion of infection with COVID-19. Treatment is valid for other high-risk measures—aerosol release (for example, broncoscopy, tracheal suction, extubation, tracheostomy, resuscitation etc.) Extubations need the same protective measures!
<i>Self-protection has highest priority</i>
<input checked="" type="checkbox"/> Early decision for endotracheal intubation
<i>Personal protective equipment</i>
<input checked="" type="checkbox"/> FFP3/2-masks (check tightness, porosity!)
<input checked="" type="checkbox"/> face shield + protective glasses + beard cap
<input checked="" type="checkbox"/> (one-time) OP-gown/overalls/(one-way gowns + water-proof aprons)
<input checked="" type="checkbox"/> two pairs of gloves
<i>Team</i>
<input checked="" type="checkbox"/> Highly experienced airway manager (no teaching intubation!)
<input checked="" type="checkbox"/> Minimal team for safe intubation (max. 3–4 persons in the room)
<i>Preparation</i>
<input checked="" type="checkbox"/> Standard monitoring, ETCO ₂ where available, iv access, video laryngoscopy, respiratory filter (between mask/tubes and respiratory bag/tubes), airway rescue plan according to the Difficult Airway Society
<input checked="" type="checkbox"/> Positioning: upper body higher
<input checked="" type="checkbox"/> Intubation checklist for minimizing delays
<i>Preoxygenation with 100% FIO₂</i>
<input checked="" type="checkbox"/> Close-fitting respiratory masks (5 min)
!! CAVE: NIV respiration leads to high aerosol contamination
CAVE: high-flow oxygen therapy (Optiflow, AirVo etc.) leads to high aerosol contamination
<i>Quick intubation/rapid sequence intubation</i>
<input checked="" type="checkbox"/> Intubation under complete relaxation
<input checked="" type="checkbox"/> Video laryngoscopy to minimize aerosol exposure
<input checked="" type="checkbox"/> Check position with etCO ₂ (where available)
!! AVOID inbetween respiration (if absolutely necessary then with minimal tidal volume)
 NO waking intubation/fiberoptic intubation (not unless absolutely indicated)
<i>Upon leaving the patient's room</i>
<input checked="" type="checkbox"/> PPE professionally divested/disposed
<input checked="" type="checkbox"/> Equipment professionally cared for/decontaminated
<input checked="" type="checkbox"/> Intensive hand hygiene
 NO touching your own head
Resource: [16–18]
PPE Personal protective equipment

Specific medicinal therapy

Nutritional therapy, thromboembolic prophylaxis and prevention of stress-related mucosal damage can be prescribed according to criteria of intensive care therapy. On the basis of various case reports, a sufficient thrombosis prophylaxis is especially to be heeded.

Usually procalcitonin stays at a normal level in virus-related illnesses. A sudden PCT increase can indicate an additional bacterial superinfection. Many studies [20] show that too many antibiotics have been prescribed based on the frequency of bacterial superinfections at the start of therapy. If clinical signs or conspicuous laboratory parameters occur (e.g. increasing PCT), antibiotic therapy according an antimicrobial stewardship program is recommended.

At the moment there is no safe specific therapy for SARS-CoV-2. Numerous antiviral and other active substances have been discussed as possible therapy options for severe adult respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) on the basis of theoretical considerations, case reports and in vitro data [21]. The level of evidence for this is considered, however, extremely low. The current data do not allow treatment recommendations for any substance.

The use of the following antiviral substances therefore can only be recommended after careful risk-benefit consideration and in the framework of studies: remdesivir, favipiravir (Avigan®), ribavirin or covalent plasma. Based on the current study situation, the use of other substances like lopinavir/ritonavir (Kaletra®) and hydroxychloroquine is not recommended [22–34]. Due to the rapidly changing study situation, it must be pointed out once again that the use of special drugs must be checked extremely carefully.

Tocilizumab (RoActemra®) or other IL-1 or IL-6 antagonists could possibly be used within the framework of studies. In this case there is a blockade of IL-6 connecting receptors. CAVE: a viral reactivation, like hepatitis B, is possible.

After such therapy, CRP as well as leucocytes are no longer valid.

Also, no sufficient statement can yet be made about the routine use of corticosteroids. While some studies [35, 36] report a positive effect, there are still no benefits found in other studies [37, 38].

The American Heart Association recommends that for patients who have tested positive for the SARS-CoV-2 virus and who are being treated for a cardiovascular disease with ACE inhibitors and angiotensin II receptor blockers, these medications should under no circumstances be discontinued. At the moment there is no scientific evidence that ACE inhibitors and angiotensin receptor blockers increase the risk of severe SARS-CoV-2 illnesses [39].

A survey of the interactions of specific therapeutics can be found under www.covid19-druginteractions.org.

Summary

The COVID-19 illnesses progress mildly in most of the cases; about 5% of the patients, however, develop a severe acute respiratory distress syndrome (ARDS). Around 3% of all COVID-19 patients need intensive care treatment, which becomes a great challenge for anesthesiology and intensive care medicine, medically, hygienically and for technical safety requirements. For these reasons, only experienced medical and nursing staff in the smallest grouping possible should be assigned. For these team members, a consistent use of personal protective equipment (PPE) is essential.

For diagnostic purposes, a nasopharyngeal/oropharyngeal swab should be taken with any suspicion of SARS-CoV-2. In cases of a questionable first finding and a high clinical suspicion for intubated patients, a bronchoalveolar lavage (miniBAL) should be done for extracting secretion from the deep respiratory tract.

A massive lymphopenia, high CRP and high LDH values indicate a complicated severe progression of the illness. Increased procalcitonin indicates a possible bacterial superinfection.

The success rates of noninvasive forms of respiration are limited. In patients with severe hypoxemia and/or clinically advanced respiratory failure, intubation and mechanical respiration with adequate PEEP values is the only possibility to stabilize pulmonary function. With unstable patients, an additional hemodynamic monitoring should be considered. With massive hemodynamic instability, hydrocortisone can be used. A sufficient thrombosis prophylaxis is to be maintained.

At the moment, there is no safe, specific therapy for SARS-CoV-2. The possible effect of various substances is being studied. The current evidence, however, does not allow for recommendations for use of any of these substances.

The recommendations found in this article are to be understood as short snapshots of the moment; all basic guidelines are works in progress and will be regularly updated as evidence levels, new study results and additional experience are gathered.

Conflict of interest M. Köstenberger, W. Hasibeder, D. Dankl, R. Germann, C. Hörmann, M. Joannidis, K. Markstaller, S.-O. Müller-Muttonen, S. Neuwersch-Sommeregger, E. Schaden, T. Staudinger, R. Ullrich, A. Valentin, and R. Likar declare that they have no competing interests.

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