Forum Sanitas
The Informative Medical Journal
Reprint from the 3rd Edition 2020

SARS-CoV-2
A medical and scientific challenge

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COVID-19 (Corona Virus Disease 2019) or SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is an RNA virus with a few 10,000 nucleotides that has the world on edge. Apparently passed from animals to humans in China in the fall of 2019, this disease has since developed into a worldwide pandemic currently affecting more than 18 million patients (1).
Those infected usually spread the virus via droplet infection, aerosols, and close physical contact. Therefore, strict implementation of basic hygiene and individual protective measures is vital. Up to 85% of patients with COVID-19 experience only a mild course of the disease, 15% suffer a severe course, and between 5% and 8% progress to a critical condition. The disease usually manifests as an airway infection with fever and cough as the leading symptoms. COVID-19 presents in a number of different ways and may affect not only the lungs but also other organs and organ systems, which can result in dramatic progression, especially in critically ill patients (2).

Introduction

COVID-19 very often produces nonspecific symptoms in the upper respiratory tract and may (usually in the second week) develop into pneumonia with respiratory failure, which may progress into life-threatening ARDS (Acute Respiratory Distress Syndrome) requiring ventilation (3). Acute lung injury may be associated with multi-organ failure in SIRS (Systemic Inflammatory Response Syndrome), which in turn is accompanied by high mortality.

Pathophysiology

According to current pathophysiological understanding, the viral load plays a central role during the first few days of the disease. In addition, the ACE2 (angiotensin converting enzyme 2) receptor density is also a major factor contributing to the severity of the disease. ACE2 is present on the membrane of a variety of cells in the human body and allows the coronavirus to invade these cells. It has been shown that patients with chronic lung disease have more of these receptors. This is seen as one of the reasons for the higher mortality in these patients (4). Patient condition can worsen within hours, especially in the second week of illness when pneumonia may develop (2). One explanation for this extraordinarily rapid deterioration is the massive deterioration of the body's immune system (cytokine storm). Here, the activity of the immune system induces a vicious circle in the patient's body: Various triggers, including SARS-CoV-2, activate the cytokine-producing leukocytes in the blood, such that the immune reaction is no longer self-limiting, resulting in an overreaction with excessive production of proinflammatory cytokines (5). The clinical symptoms are caused by the strong systemic inflammatory reactions. Since lab tests often reveal significantly elevated inflammatory parameters with concomitant shortage of lymphocytes, lymphocytopenia must also be considered as a marker for poor prognosis. It is now widely accepted that this overreaction of the immune system can trigger life-threatening complications such as ARDS, thrombosis and other endotheliites.

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Admission criteria for intensive care monitoring

Inpatient monitoring is recommended if oxygen saturation (SpO_2) is < 95% or the patient has relevant risk factors, such as high blood pressure and diabetes mellitus. Admission to the intensive care unit usually results from dyspnea with an increased respiratory rate > 30 breaths/min and hypoxemia as the leading symptom. At this time imaging often already shows pulmonary infiltration/consolidation.

COVID-19 patients should be admitted to the intensive care unit if one of the following criteria is met:

- Hypoxemia SpO_2 < 90% (under 2 - 4 liters of oxygen/min with no prior treatment) and dyspnea
- More than 30 breaths per minute
- Systolic blood pressure ≤ 100 mmHg
- Elevated lactate levels.

Medication strategies

At present, medication in COVID-19 disease is founded on very limited evidence. A large-scale clinical trial (RECOVERY) will compare different drug treatment regimens. While no outcomes have been published to date, preliminary results have already been reported: The RECOVERY trial has enrolled 175 hospitals in the United Kingdom with over 11,000 patients. This open multicenter multi-armed trial explores different drug regimens (lopinavir-ritonavir, tocilizumab, dexamethasone,

azithromycin, hydroxychloroquine) in hospitalized and ventilated COVID-19 patients. In a first press release it was noted that ventilated patients on 6 mg dexamethasone per day administered for 10 consecutive days showed a clear survival benefit versus standard treatment. Based on the preliminary data of the RECOVERY trial and despite the still ongoing discussion of the trial, the German Respiratory Society recommends dexamethasone 6 mg/d p.o. or i.v. for up to 10 days in patients with COVID-19 and manifest severe respiratory failure requiring oxygen or ventilation, unless contraindicated. It is important to note the need for close monitoring and control of blood glucose and sodium serum levels, regular assessment of potential superinfections, and the increased risk of gastrointestinal hemorrhage (7, 8).

Remdesivir (9), a protease inhibitor, currently appears to have a positive effect on the course of disease in mildly ill patients with respiratory failure. It was demonstrated that this could shorten the length of stay in hospital even in moderately to seriously ill patients. Since in one arm of the RECOVERY trial other medications, such as lopinavir-ritonavir, did not offer any benefit (10), this medication is not recommended at present.

Antibody treatments

There are two different approaches in antibody treatment: Polyvalent intravenous (IVIg) and anti-COVID-19 hyperimmunoglobulins from convalescent plasma.

Intravenous immunoglobulins

IVIg is a large pool of various human antibodies obtained from the plasmas of healthy donors. Currently, IVIg are used as a standard treatment in a number of conditions requiring immunomodulation. Based on this experience, the FDA has approved a pivotal study for the treatment of COVID-19 patients. Retrospective data already exist from Wuhan, Heidelberg, San Diego, New York and many other international centers (11). Experience has shown that high-dose IVIg can markedly reduce the severity of COVID-19 infection, if the immunoglobulins are applied early when the respiratory situation deteriorates. Almost all patients in the retrospective analyses achieved clinically significant improvement in their health after treatment with polyvalent IVIg. These patients showed a reduction in the inflammation parameter CRP (C-reactive protein), which correlated with the severity of the disease, mortality, and O_2-saturation. IVIg administration also lowered fever (Fig. 1).

Based on these promising data, the pharmaceutical research company Octapharma is conducting a phase-3 trial in the USA studying the respiratory situation, lung function, quality of life, and mortality in affected patients under immunoglobulin treatment. A total of 208 patients in 10 US study sites will be enrolled in this trial. The retrospective data already available suggest a high degree of efficacy and evidence of the immunoglobulin treatment.

Anti-COVID-19-hyperimmunoglobulin

Patients who have recovered from a COVID-19 infection usually express specific antibodies. Specific antibodies can be extracted from the plasma of these patients, which are then administered to patients with severe course of the disease. A pilot study examined the safety and efficacy of convalescent plasma in 10 patients and found that the clinical situation improved, the lymphocyte count increased, and the CRP level declined. Thus, the administration of specific immunoglobulins also appears to have a role to play. However, there are a number of hurdles to overcome in this context: First of all, numerous convalescent donors are needed to produce this hyperimmune serum; in addition - according to current findings - the number of specific antibodies already decreases rather quickly in the first few months of the disease, with the result that the plasma of the recovered COVID-19 patients may not contain an adequate quantity of antibodies. Furthermore, no protective titers are known at present. Further trials are planned to demonstrate the effectiveness and efficacy of hyperimmune serum from convalescent donors.

Ventilation strategies and treatments in hypoxemic respiratory failure

In case of hypoxia with oxygen saturation levels below 95%, oxygen administration via nasal probes or so-called high-flow oxygen administration should be given priority. In cases of progressive deterioration of the condition and increased oxygen demand, non-invasive CPAP (continuous positive airway pressure) ventilation

In severe coronavirus infections, the so-called **cytokine storm** plays a major role in the emergence of life-threatening processes. Cytokine storm is characterized by the uncontrolled release of cytokines and thus an overreaction of the body's immune defenses. Cytokine storm may result in severe inflammatory reactions in the lungs and other organs, with ultimately fatal outcome in some patients. **Hence, the therapeutic use of immunomodulatory intravenous immunoglobulins (IVIg) appears advisable.** Retrospective studies already demonstrated in some patients with severe COVID-19 course that the administration of high-dose IVIg had a positive effect on the course of the disease (13, 14). To investigate the effectiveness and efficacy of IVIg as a therapeutic option in severe courses of infection, Octapharma has initiated a prospective, randomized, double-blind, placebo-controlled phase-3 study with 208 patients in 10 US study sites. In this trial, COVID-19 patients on the ICU are treated with IVIg (octagam 10%). The analyses will study in detail whether the administration of IVIg helps to stabilize and/or improve the clinical condition of the patients thus treated. The following parameters will be considered in particular: Mortality, level of oxygen saturation, duration of intubation, duration of mechanical ventilation, and changes in clinical lab parameters (15). Preliminary results are expected in the fourth quarter of 2020.

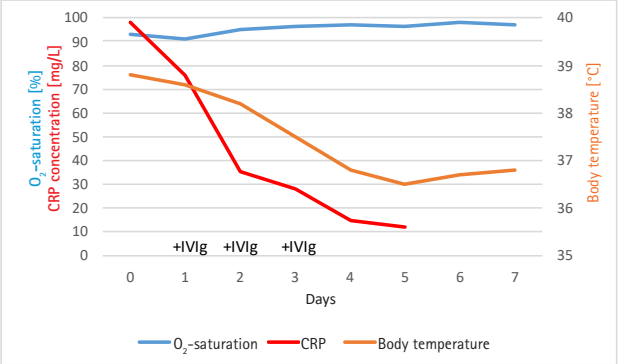

Figure 1: Course of O_2 saturation, CRP, and body temperature after IVIg administration on days 1, 2, and 3 in a 34-year-old patient.

via nasal mask or non-invasive oxygen administration should be employed. If these measures fail and the acute respiratory condition deteriorates further, invasive ventilation should be initiated. This requires dedicated settings of the ventilators, since early phase pulmonary COVID-19 infection differs significantly from classic ARDS. This is due to the limited lung compliance at the onset of the disease. If acute lung failure develops, the typical ventilation patterns should be applied (tidal volume, 6 mL/kg/standard body weight), inspiratory airway pressure less than 30 cm H_2O. In patients with severe ARDS and refractory hypoxia, extracorporeal membrane oxygenation (ECMO treatment) is one therapeutic option to stabilize gas exchange. It has also been shown that ventilation in the prone patient has a certain positive effect, which suggests that appropriate patient repositioning should also be considered. In addition to ventilation strategies, patients should be administered low-molecular-weight heparin to prevent thromboembolic events, since these are a common complication (12).

Summary

15% of COVID-19 patients suffer a severe course, and about 5% require intensive care treatment. Retrospective data have revealed that early administration of polyvalent immunoglobulins can help stabilize the clinical situation. Otherwise, based on the current evidence, the administration of remdesivir is currently recommended in moderately severe cases, and dexamethasone in patients requiring ventilation. In terms of respiratory failure, oxygen administration, also by means of high-flow application, is considered an effective measure in these patients. If this does not stabilize the patient, intubation and ECMO treatment is required. It has become apparent that these patients clearly benefit from treatment in specialized centers with particular expertise. Since the current treatment recommendations are not yet based on adequate evidence, adjustments can only be expected once the current trial activities have been completed and evaluated.

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■ **Further information**

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2020-0-10-C-19