AWMF-Register-Nr. 113/001

Recommendations for Treatment of Critically Ill Patients with COVID-19 – version 3

S1 Guideline

Last amended 21/07/2020 (Version 3)

Stefan Kluge[1,2,3,10], Uwe Janssens[1,2,10], Tobias Welte[1,3,10], Steffen Weber-Carstens[2,4,10], Gereon Schälte[4], Bernd Salzberger[5], Petra Gastmeier[6], Florian Langer[7], Martin Welper[4], Michael Westhoff[3], Michael Pfeifer[3], Florian Hoffmann[2,8], Bernd W. Böttiger[2,9], Gernot Marx[2,4,10], Christian Karagiannidis[1,2,3,10]

Primary responsibility:

[1]Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN), Berlin

[2]Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI), Berlin

In cooperation with:

[3]Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP), Berlin

[4]Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI), Nürnberg

[5]Deutsche Gesellschaft für Infektiologie (DGI), München

[6]Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM), Münster

[7]Gesellschaft für Thrombose und Hämostaseforschung (GTH), Köln

[8]Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ), Berlin

[9]Deutscher Rat für Wiederbelebung (German Resuscitation Council; GRC), Ulm

[10]ARDS Netzwerk Deutschland, Berlin

Corresponding Author:

Prof. Dr. med. Stefan Kluge

Klinik für Intensivmedizin

Universitätsklinikum Hamburg-Eppendorf

Martinistr. 52

20246 Hamburg

skluge@uke.de

Table of Contents

Abstract

Since December 2019, a novel coronavirus (Severe Acute Respiratory Syndrome - Corona Virus - 2, SARS-CoV-2) has rapidly spread around the world resulting in an acute respiratory illness pandemic. The immense challenges for clinicians and hospitals as well as the strain on many healthcare systems has been unprecedented.

The majority of patients present with mild symptoms of Coronavirus Disease 2019 (COVID-19). However, about 5-8% become critically ill and require intensive care treatment. Acute hypoxemic respiratory failure with severe dyspnoea and an increased respiratory rate (>30/min) usually leads to ICU admission. At that point, bilateral pulmonary infiltrates are typically seen. Patients often develop a severe Acute Respiratory Distress Syndrome (ARDS). So far, Remdesivir and Dexamethasone have shown clinical effectiveness in severe COVID-19 in hospitalised patients. The main goal of supportive therapy is to ascertain adequate oxygenation. Invasive mechanical ventilation and repeated prone positioning are key elements in treating severely hypoxemic COVID-19 patients.

Strict adherence to basic infection control measures (including hand hygiene) and correct use of personal protection equipment (PPE) are essential in the care of patients. Procedures that lead to formation of aerosols should be carried out with utmost precaution and preparation.

1. Preamble

This is the second update of this guideline, published on 21/07/2020 (version 3).

Information on the recently published RECOVERY study on dexamethasone and on the official approval of Remdesivir for COVID-19 as well as details regarding breathing system filters (HME versus HEPA) and aspects of care for paediatric patients were added.

These recommendations aim to give guidance to physicians treating COVID-19 patients on their ICUs. We acknowledge that the pandemic is in a dynamic stage and that experience and scientific evidence will grow. Comprehensive information on the pathogen and the trajectory of the pandemic is available online through the Robert-Koch-Institut (RKI, www.rki.de). We strongly recommend a multi-disciplinary approach in the management and treatment of COVID-19 patients. Aside from Intensive Care physicians and nurses, infectious disease and infection control specialists need to be part of the team.

2. Introduction

The first cases of the novel coronavirus (Severe Acute Respiratory Syndrome - Corona Virus - 2, SARS-CoV-2) were noted in China in December 2019. Since then, SARS-CoV-2 has been rapidly transmitted around the world resulting in a pandemic. The clinical picture of the infection is called Coronavirus Disease 2019 (COVID-19). Transmission of SARS-CoV-2 usually occurs via droplet infection during close contact. Therefore, a strict implementation of basic infection control measures such as hand hygiene, and the use of personal protection equipment (PPE) are essential.

3. Diagnostic Approach

3.1. Specimens and Testing

The detection of SARS-CoV-2 is carried out from a nasopharyngeal or oropharyngeal swab using real-time reverse transcriptase-polymerase chain reaction (RT-PCR). A patient with a negative test should be retested if there is a high clinical suspicion that they have contracted the virus. The swab might become negative while there is still infectious viral shedding in the lower airways at a later stage of the disease (pneumonia, ARDS). A PCR of endotracheal aspirates might be helpful in those cases.

At this point in time antibody testing primarily serves an epidemiological purpose. In our current understanding, detection of SARS-CoV-2 specific antibodies in serum indicates an exposure to SARS-CoV-2 but does not yet allow safe determination of the level of infectiousness or immunity (1).

3.2. Clinical Features

In Germany, the median age of patients with COVID-19 is 49 years (2), of those admitted to the ICU it is 63 years (3). Women and men are generally affected at a similar rate, 52% versus 48% respectively. However, men do suffer two times more often from severe COVID-19 disease than women, and their mortality is higher (2). Patients in need of in-hospital treatment usually have significant pre-existing medical conditions, most often regarding the cardiovascular system, e.g. hypertension, diabetes mellitus, chronic lung disease and obesity (4-6).

Frequently, COVID-19 presents as an airway infection with fever and dry cough as key features. The only quasi pathognomonic symptom of COVID-19 is anosmia, which occurs in 10-20% of the patients. In 81% of the patients the disease takes a mild course, 14% of the patients become severely ill, and, approximately 5% of the patients become critically ill (7). Severe dyspnoea with an increased work of breathing (respiratory rate > 30/min) and hypoxemic respiratory failure typically lead to admission to ICU. At that stage, bilateral pulmonary infiltrates can often be seen on imaging (8).

Admission to ICU should be considered in COVID-19 patients presenting with the following clinical features:

- hypoxemia SpO_2 < 90% on 2-4 L/min oxygen (without previous oxygen therapy) plus dyspnoea
- respiratory rate > 25-30/min
- systolic blood pressure ≤ 100 mmHg
- elevated serum lactate

Severely affected patients may develop ARDS or, although not as often, bacterial superinfection and septic shock. Many critically ill patients on ICU need to be treated with invasive ventilation (3,9). Further complications seen in COVID-19 patients are arrythmias, myocardial dysfunction and pulmonary embolism as well as acute kidney failure and multi-organ dysfunction. On average, it takes approximately 10 days from showing first symptoms to ICU admission (10). Median ICU length of stay is 9 days (3), in ventilated patients 18 days (5).

3.3. Laboratory Changes

In 80% of COVID-19 patients there is apparent lymphocytopenia, and, in one third of those patients this is accompanied by leukopenia. Most of the patients have elevated CRP but normal levels of Pro-Calcitonin. However, a bacterial superinfection might trigger a significant increase in Pro-Calcitonin (11). Thrombocytopenia, and, an elevation of D-Dimers and LDH

are found in approximately 40% of the patients. Based on current knowledge, increased D-Dimers, persistent lymphocytopenia and elevated LDH indicate a severe course of the disease and a limited prognosis (5). A small portion of patients also present with elevated troponin, of which the clinical implications are as yet unknown.

3.4. Imaging

Conventional chest radiographs show bilateral infiltrates in COVID-19 patients treated on ICU. Even in early stages of the disease, Computer Tomography (CT) can reliably detect typical bilateral subpleural ground-glass opacities and consolidation of the lungs, whereas pleural effusions and lymphadenopathies are rare (12, 13). However, CT findings are not COVID-19 specific and can be found in other viral pneumonias as well.

Due to the potential risks for health care workers and patients, we advise to only perform CT imaging in ICU patients when absolutely necessary for clinical decision making, e.g. in suspected pulmonary embolism (14). Bedside imaging, e.g. ultra-sonography, should be preferred otherwise, especially to assess the course of the disease during ICU admission.

4. Infection Control

Patients should preferably be treated in isolation rooms, ideally with a functional anteroom for donning and doffing PPE. As the epidemic/pandemic progresses, isolation of patients in cohorts is reasonable.

Strict spatial separation of patients positive for SARS-CoV-2 and others should be carried out on the ward level. If possible, patients should be allocated into three different areas with distinct separation in terms of space and personnel:

- COVID-19 area (all patients positive for SARS-CoV-2)
- area for suspected cases
- non-COVID-19 area (all patients negative for SARS-CoV-2 and asymptomatic)

Room ventilation systems and air conditioning with active venting should not be turned off. If necessary frequent aeration by window ventilation, which reduces aerosol transmission, can be undertaken. Aeration between two rooms should be avoided.

Patients with COVID-19 should only be seen and cared for by trained personnel who do not have contact to other non-COVID-19 patients. The number of people working or visiting at bedside should be kept to a minimum and be tailored to the actual patient needs – this also includes implementation of restrictions to visits by family and friends.

Personnel working at bedside must strictly adhere to basic infection control measures such as hand hygiene and consequently follow instructions on the use of personal protection equipment (PPE). According to the RKI, correct PPE consists of an impervious gown, gloves, tight-fitting facemask (FFP2 or FFP3 in case of strong exposure to aerosols due to certain procedures, e.g. intubation, bronchoscopy) as well as goggles. It is important to frequently train health care workers on structured donning and removing of PPE, especially on tight mask-fitting and sequential hand disinfection.

Comprehensive recommendations on infection control (rooms, protection of personnel, disinfection, cleaning, waste handling, patient transport and visitor regulations) can be found online on the website of the RKI (15). Local guidelines and standard procedures for hospitals should be implemented by a multi-disciplinary expert panel according to the local situation.

It seems reasonable to lift isolation requirements for ICU patients post COVID-19 based on the following scenarios:

1. Patient with endotracheal tube or tracheostomy
    - first symptoms > 14 days ago
    - two sets of two negative SARS-CoV-2 tests (naso- or oropharyngeal swab plus endotracheal aspirate, simultaneously carried out)

2. Patient extubated or on non-invasive ventilation
    - first symptoms > 14 days ago
    - two sets of two negative SARS-CoV-2 tests (nasopharyngeal swab plus oropharyngeal swab, simultaneously carried out)

5. Management of Acute Hypoxemic Respiratory Failure

5.1. Oxygen Therapy, High-Flow Oxygen Therapy, Non-Invasive Ventilation

First line options to support patients in respiratory failure and hypoxemia with oxygen are simple nasal cannula, Venturi masks and high-flow nasal cannula (HFNC; figure 1) (16). As gas exchange worsens progressively and oxygen demand increases, CPAP therapy, non-invasive ventilation (NIV) or invasive ventilation need to be considered. The overarching goal is to ascertain adequate oxygenation. It is recommended to aim for $SpO_2 \geq 90$ % or $paO_2 > 55$mmHg, respectively (17,18).

High-flow nasal cannula is often used in hypoxemic respiratory failure and reduces the need for intubation without affecting mortality (19). Using NIV in moderate and severe ARDS fails in up to 50% of the patients, which is associated with a mortality as high as 50% in severe ARDS (20, 21). Not only the level of severity but also the extent of hypoxemic failure predicts NIV failure: a $PaO_2/FiO_2 \leq 150$ mmHg was shown to be a critical threshold for increased mortality (22). Additionally, high tidal volumes (> 9,5 ml/kg BW) during NIV within the first 4 hours of treatment predict NIV failure (23). Consequently, as those patients can deteriorate quickly, continuous monitoring and readiness for intubation is mandatory. Therefore, HFNC and NIV in acute respiratory failure should preferably be used in an ICU setting. In case of progressive disease and clinical worsening despite all measures, intubation and invasive ventilation should be carried out timely and without delay if in the patient´s interest and will.

5.1.1. Aerosol Formation

Depending on the applied flow and pressure, both HFCN and NIV, are associated with increased aerosol formation, which in turn potentially increases risk for virus transmission in COVID-19 patients (24, 25). As a principle, every breath leads to aerosol formation, the extent of it correlates with the depth of the breath (26). Based on current knowledge, an increased amount of infectious aerosol particles is only detectable in patients on vented-NIV (versus non-vented NIV) and patients with a high load of secretions (27). Studies on exhaled air and particle dispersion during HFNC and NIV were not able to show substantial exposure to exhaled air in more than one meter of distance to the face of the patient (28-30).
However, it is absolute necessary for everyone working with COVID-19 patients to use their PPE correctly, especially ensuring a tight mask fit, while using HFNC and NIV (14). The proper fit of the nasal high-flow cannula and the NIV mask on the patients' end is of course important to reduce aerosol formation in the first place (28). During HFNC therapy patients wear an additional face mask on top of the cannula (31). Studies using computer simulation models showed that this technique can reduce particle dispersion during exhalation (32). It is unclear though whether this has an impact on the performance of HFNC therapy. During NIV therapy air leakage needs to be kept at a minimum. Therefore, we recommend using non-vented oro-nasal face masks, full-face masks or helmets, especially in COVID-19 patients. Respirators used in those patients should preferably be operated with dual-limb tubing to reduce contamination of the environment. When using single-limb tubing a viral filter needs to be placed in between the interface and the exhaust systems' whisper swivel or expiration valve (16). This reduces aerosol dispersion, even in comparison with spontaneous breathing (27).

In conclusion, neither the use of HFNC or NIV in severe hypoxemia nor early intubation in less severely affected patients in order reduce exposure for personnel seem to be justified in

patients with a SARS-CoV-2 infection. We recommend to only use HFNC or NIV in patients with COVID-19 related acute hypoxemic respiratory failure on clear indication and with all necessary precautions. In patients with severe hypoxemia (PaO_2/FiO_2 ≤ 150 mmHg) and a respiratory rate > 30/min, intubation and invasive ventilation should be preferred as delayed intubation in NIV failure worsens outcome. It is important to avoid emergency intubation in order to keep the risk of aerosol exposure and transmission of the virus at a minimum.

5.2. Interventions

Due to the risk of aerosol formation, airway procedures (intubation, bronchoscopy, open suction, bag ventilation, tracheostomy) should only be performed with appropriate airborne precautions PPE (including gown, gloves, FFP2/FFP3 masks and goggles) and if absolutely necessary to protect personnel from exposure (Table 1). The PPE may be complemented by a protective visor (33,34).

5.3. Intubation

Endotracheal intubation is considered a high-risk intervention in patients with suspected or confirmed SARS-CoV-2 infection (35). Preparation and execution, especially in regard to hygiene precautions, need to follow specific protocols that were sufficiently communicated and practiced in advance (36, 37). Therefore, if possible, intubation should be performed electively and be well-planned; also, the number of people at the bedside should be kept to a minimum. The use of a transparent plastic sheet or a so-called intubation box to cover the patient during intubation has been debated with controversy but may be a reasonable option to reduce aerosol formation (38, 39).

If possible, intubation should be performed by the most experienced physician to minimize intubation attempts and time needed (40). It is recommended to use video-laryngoscopy for intubation to increase distance between physician and patient during intubation given it is available and personnel are already trained in its use. We strongly encourage the use of a stylet for intubation, especially in video-laryngoscopy it is imperative. Due to possible aerosol formation awake fibre-optic intubation should be avoided where possible. It may only be considered when options for other techniques are limited, e.g. a difficult airway. To minimize aerosol formation, we suggest avoiding bag mask ventilation. Pre-oxygenation in the spontaneous breathing patient can be carried out with a tight-fitting face mask using a bi-manual technique and application of a PEEP (positive end-expiratory pressure) of ≤ 5cmH2O. Intubation should be performed as a rapid sequence induction. After administration of the neuromuscular blocking agent and consecutive apnoea, we suggest turning off gas flow just before removing the mask in order to reduce aerosol dispersion. Immediately after intubation and before connection to the respirator, an HME filter should be placed on the tube. In general,

it is recommended to only use high quality viral filters with an efficiency of ≥ 99,9%, which are well established and readily available on the market (41). In theory, using mechanical HEPA filters may have advantages due to their lower permeability for smaller particles. However, to date there has been no specific research regarding the use of conventional filter systems in the context of COVID-19.

In case of an anticipated or unanticipated difficult intubation, management needs to be adjusted according to the S1-guideline on airway management (42). If intubation is not feasible, a supraglottic airway device, e.g. laryngeal mask, should be established. In the event of a “cannot intubate, cannot oxygenate” (CICO) situation, it is recommended to proceed directly to cricothyrotomy.

5.4. Extubation

Preferably, patients are extubated avoiding coughing or gagging and without any inflation manoeuvres. Closed endotracheal suction just before extubation can be considered. We recommend leaving the HME filter on the tube for extubation and discard it together afterwards. Ideally, patients show sufficient oxygenation with oxygen face mask on low-flow oxygen (40, 41).

5.5. Invasive Ventilation and Adjuvant Treatment

Due to the lack of randomized studies regarding ventilation strategies in COVID-19, current recommendations refer to the latest guidelines for invasive ventilation in acute respiratory failure (17, 43).

Especially in the early phase of COVID-19, lung mechanics are different from typical ARDS and show specific features. Lung compliance for instance is less impaired in the early stages. And, early on, hypoxemia seems to be due to a pronounced ventilation perfusion mismatch rather than lack of recruitment (44, 45). This is further aggravated by vascular complications that impair microcirculation significantly (46).

For invasive ventilation in COVID-19 we recommend using closed inline suction catheters. In patients with ARDS, it is generally recommended to use a tidal volume (TV) of ≤ 6 ml/kg ideal body weight and a plateau pressure of no more than 30 cm H_2O. At this point in time, there is no strict guidance on PEEP in COVID-19 due to lack of robust data especially for the early stages of the disease. The PEEP therefore needs to be adjusted according to clinical findings and individual patient situation. However, from a pathophysiological standpoint it may be reasonable to avoid high PEEP in COVID-19 patients. In case the patient develops a classic ARDS pattern, PEEP can be adjusted according to the ARDS network tables (43). In severe ARDS with a P_aO_2/F_iO_2 ≤ 150 mmHg, prone positioning should be administered consistently

for 16hrs. If severe hypoxemia persists, prone positioning needs to be repeated. In individual cases, inhaled NO, the administration of neuromuscular blocking agents and recruitment manoeuvres may be considered as options for bridging to recovery. Where available, in patients with severe ARDS and refractory hypoxemia (P_aO_2/F_iO_2 < 80 or 60 mmHg) veno-venous extracorporeal membrane oxygenation (vvECMO) may serve as a therapeutic option to ensure gas exchange. As it is a very complex and resource intensive treatment, all other measures should have been exhausted before considering ECMO, and thorough evaluation of risks and benefits, including the presumed patient will, is warranted.

5.6. Tracheostomy

In the context of invasive ventilation, tracheostomy may expedite weaning from the respirator and freeing up ICU capacities (47-49). Furthermore, tracheostomy helps to minimize the use of sedative medication and facilitates weaning into spontaneous breathing, subsequently reducing the risk for critical-illness myopathy or polyneuropathy in long-term ventilated patients (50). However, patients with improved organ function, specifically lung function, should be assessed for extubation and weaned from the ventilator when meeting the necessary requirements (51). Yet, the risk for extubating failure is high in COVID-19 virus pneumonia and management for re-intubation is associated with a higher risk of aerosol formation (35). Despite recommendations for some specific circumstances, e.g. trauma patients, the decision for or against tracheostomy has to be made on an individual basis (52, 53). Regarding the time point, early tracheostomy in ventilated critically ill patients is not recommended by current guidelines (43). It is important to keep in mind that viral load decreases over time in COVID-19. However, laryngeal damage and dysfunction, ventilator-associated atrophy of accessory muscles of respiration, and possible regaining of communication favours tracheostomy at an earlier time point (48). For patients still experiencing multi-organ failure, however, tracheostomy may be considered at a later stage.
Patients need to be respiratory stable and able to sustain apnoeic episodes during the procedure before being considered for tracheostomy. Possible techniques are percutaneous dilatational tracheostomy, conventional surgical tracheostomy or a so-called modified hybrid tracheostomy. Percutaneous dilatational tracheostomy is a fast and uncomplicated bed-side approach in the ICU setting performed without surgical aid. The tight seal after placement of the cannula is another benefit of this technique. Reasons to follow a surgical approach on the other hand are the following: controlled surgical preparation of the trachea with reduced risk of contamination; safe airway even in the case of dislocation - for instance in prone positioning; possible avoidance of aerosol forming bronchoscopy during the procedure; and, obesity, a common pre-existing condition in COVID-19 patients, as a relative contraindication for percutaneous dilatational tracheostomy.

Like for intubation, the number of personnel at the bedside needs to be kept to a minimum during the procedure and the most experienced physician should perform the tracheostomy. Individual risk factors of the patient as well as local circumstances and expertise have to be considered when making decisions around tracheostomy and choosing a suitable technique.

6. Cardiac Arrest and Cardiopulmonary Resuscitation

Studies from China showed respiratory failure as the major cause for cardiac arrest in COVID-19 patients, the initial rhythm often being asystole (54). It is likely that aerosol formation and dispersion occurs during chest compression and airway management, which emphasises the need for proper use of PPE during cardiopulmonary resuscitation (55). Defibrillation presumably does not cause aerosol formation. It is not recommended to check for audible breathing and lowering one´s own face towards the patient's while determining cardiac arrest. If a defibrillator is readily available, it is suggested to check for shockable rhythms and then administer three sequential shocks when indicated. In the interim, additional personnel can put on their PPE. However, it is important to keep the number of personnel at bedside to a minimum during resuscitation to reduce potential exposure (55). Airway management should be carried out by the most experienced physician, where endotracheal intubation is preferred over other techniques. We recommend two-person bag mask ventilation, where one person manages the mask and the airway while the other one squeezes the bag to ventilate the chest in between chest compressions. It is suggested to perform chest compressions and ventilation in a 30:2 ratio when using supraglottic airway devices as well. Viral filters should be used in both, manual and mechanical ventilation. In case of prolonged cardiopulmonary resuscitation, a mechanical chest compression device may be considered (55). Non-intubated patients should be turned into a supine position if cardiac arrest occurs while the patient is in prone positioning. In intubated patients, cardiopulmonary resuscitation may be feasible in the prone position. In this case chest compressions are to be applied in between the inferior borders of the shoulder blades (55). However, the patient has to be turned if diastolic blood pressure remains below 25 mmHg or other issues occur in the prone position. Defibrillation pads can be placed anterior-posterior or bi-axillary when patients remain in prone position during resuscitation. Since COVID-19 patients have a high incidence of deep vein thrombosis and pulmonary embolism, thrombolytic therapy should be considered where other causes of cardiac arrest are excluded (56).

7. Prevention of Venous Thromboembolism

Thromboembolic complications are common in COVID-19; they are usually of venous origin but can affect the arterial system as well (57, 58). Therefore, all hospitalized patients should receive primary venous thromboembolism prophylaxis with low-molecular-weight heparin

(LMWH), dose-adjusted to high risk groups. In case of heparin intolerance or confirmed heparin-induced thrombocytopenia, fondaparinux serves as an alternative. However, observational studies suggest that, especially in critically ill patients, prophylactic doses of LMWH may be insufficient. Weighing in the individual risk of major bleeding and renal function, a more intensified anticoagulation regime, e.g. with half-therapeutic, intermediate doses of LMWH, may be considered. We do not recommend routine use of therapeutic doses of anticoagulation without confirmed venous thromboembolism or outside of ECMO treatment. However, it can be reasonable in the individual case with a high level of suspicion, e.g. patients with high D-dimers plus/or acute worsening of gas exchange where timely imaging is not available. Because the development of pulmonary microthrombi is a specific feature of ARDS associated with COVID-19 (46), therapeutic anticoagulation can be considered for mechanically ventilated ICU patients on an individual basis as well (59). In that case, potential risks (e.g. pulmonary haemorrhage) need to be thoroughly weighed against the benefits. If renal function is severely impaired (cGFR < 30 ml/min), anticoagulation with unfractionated heparin (UFH) is preferred. When aiming for therapeutic anticoagulation, anti-Xa activity for UFH may be used as a marker for effectiveness in case aPTT does not respond adequately. Development of disseminated intravascular coagulation (DIC) with hyperfibrinolysis or consumptive coagulopathy is rare and occurs mostly in later stages of the disease. In order to reference COVID-19 related changes in haemostatic parameters appropriately and according to their specific pathophysiological basis, two new terms were recently introduced: COVID-19-associated coagulopathy (CAC) (60), and, pulmonary intravascular coagulopathy (PIC) (61). It is reasonable to monitor relevant markers, e.g. platelets, prothrombin time/INR, fibrinogen, D-dimers and antithrombin, in patients with COVID-19 and complex coagulopathies.

8. Therapy

8.1. Antibiotic Therapy and general Treatment Principles

As a principle, it is recommended to sample at least 2 blood cultures sets (aerobic and anaerobic at any one time) at the time of admission to ICU and whenever the patient worsens (62). In patients suspected of having a bacterial superinfection an empiric broad-spectrum antibiotic therapy should be started as soon as possible. A prophylactic antibiotic treatment merely on the basis of a SARS-CoV-2 infection is not recommended.

Fluid management should be handled restrictively, especially in cases with no signs of shock or tissue malperfusion, as fluid overload further impairs oxygenation.

8.2. Specific Pharmacologic Therapy

As our understanding grows constantly and new evidence may surface rapidly, the following recommendations for pharmacological interventions in COVID-19 should be tentatively interpreted and reassessed frequently.

There are two approaches concerning medical therapy for severely affected, hospitalised COVID-19 patients: anti-viral treatment and modulation of the immune response. In the following, we summarise data on pharmacologic therapies published in at least one case series or cohort study. In Europe, official approval for treatment in COVID-19 has so far only been granted for Remdesivir.

Anti-Viral Therapies

Chloroquine/Hydroxychloroquine plus Azithromycin:

Potential benefits: In-vitro proven efficacy, in-vivo anti-viral effectiveness is unclear. Impact on the clinical course has not been sufficiently investigated for hospitalised patients yet; there is only one non-peer-reviewed published study showing potential advantages of chloroquine in mild to moderate disease (63-66).

Potential risks: Severe side effects of Hydroxychloroquine are cardiac toxicity and retinal damage (high dose and prolonged treatment). Increased mortality for Chloroquine-diphosphate (2x600mg/d) in critically ill patients. Side effects of Azithromycin include drug interactions, prolonged QT-syndrome, and arrhythmias

Assessment: Not recommended outside of clinical studies.

Interferon beta-1b

Potential benefits: In-vitro anti-viral activity against MERS-CoV. A randomized phase-2 trial showed improved anti-viral effectiveness in combination with Lopinavir and Ritonavir compared to Lopinavir and Ritonavir alone. So far, no evidence on improved clinical outcomes (67).

Potential risks: Can trigger influenza-like symptoms and hematopoietic dysfunction.

Assessment: Not recommended outside of clinical studies.

Lopinavir/Ritonavir

Potential benefits: Modest in-vitro anti-viral activity. Randomised trial with small cohort size found no significant clinical advantage (68).

Potential risks: May cause severe drug interactions due to inhibition of CYP-3A4. Contraindicated in severe liver failure. Potential side effects include nausea and diarrhoea.

Assessment: Not recommended outside of clinical studies.

Remdesivir

Potential benefits: In-vitro good anti-viral activity. No clinical advantage in mild to moderate COVID-19 cases, but high-quality multinational, randomized, placebo-controlled trial showed clinical effectiveness for Remdesivir in severe disease (69, 70).
Potential risks: Hepatotoxicity. Possible side effects not yet fully understood and categorised.
Assessment: May be considered in severely affected hospitalised COVID-19 patients with pulmonary manifestations.

Modulation of the Immune Response

Steroids

Potential benefits: There has been controversy regarding steroids in ARDS. Especially in viral ARDS, e.g. SARS and influenza, steroids showed negative effects. Recently, results of the RECOVERY trial from the UK were published in the *New England Journal of Medicine*, where hospitalised patients were treated with either dexamethasone (6mg/d once daily for 10 days) or standard therapy (71). The primary endpoint was 28-day-mortality. In total, 2104 patients received dexamethasone treatment and 4321 standard therapy. Overall, 482 patients died during the study period: 22.9% of those treated with dexamethasone and 25,7% of those with standard therapy ($p<0.001$). The effect was greatest in mechanically ventilated COVID-19 patients (29,3% versus 41,4% mortality), even patients just on oxygen therapy +/- NIV without invasive ventilation benefited (23,2% versus 26,2% mortality) significantly. For patients less severely affected without oxygen therapy of any kind, dexamethasone did not have an advantage but rather showed negative effects.
Potential risks: Immunosuppression, increased risk of bacterial superinfection.
Assessment: It is recommended to use dexamethasone (6mg/d once daily for 10 days) in ventilated patients with COVID-19.

Tocilizumab

Potential benefits: Competitive binding to soluble and cell surface IL-6-receptors leads to inhibition of IL-6 signal transduction pathways and attenuation of the inflammatory response. Cohort studies showed reduced rates of fever, a decrease in CRP and increase of lymphocyte count. Clinical effectiveness has not yet been shown (72,73).
Potential risks: Immunosuppression, increased risk of bacterial superinfection.
Assessment: Not recommended outside of clinical studies.

Anakinra

Potential benefits: Competitive binding to IL-1 receptor inhibits its signal transduction pathways. Effectiveness has been proven in case series of secondary hemophagocytic

lymphohistiocytosis and macrophage activation syndrome. A clinical benefit in COVID-19 has not yet been shown (74).
Potential risks: Immunosuppression, increased risk of bacterial superinfection.
Assessment: Not recommended outside of clinical studies.

Others

Convalescent plasma

Potential benefits: In theory, there is, analogue to convalescent plasma in other infectious diseases, e.g. Ebola, a possible advantage in clinical treatment of COVID-19. However, this has not yet been investigated in depth (75,76).
Potential risks: Hypersensitivity reaction (rare).
Assessment: Not recommended outside of clinical studies.

Summary

So far, clinical effectiveness has only been shown for Remdesivir and dexamethasone in hospitalised patient with severe COVID-19. In Europe, Remdesivir was approved for treatment of SARS-CoV-2 related pneumonia that requires oxygen therapy on July 3rd, 2020. Patients with hypoxemia and need for oxygen treatment benefit the most, there is no robust data available on ventilated patients yet. On the other hand, dexamethasone reduces mortality especially in mechanically ventilated COVID-19 patients.
At this time point, we do not recommend the use of any other pharmacological treatment option, neither anti-viral nor immunomodulatory, outside of clinical trials and appropriate clinical settings. The University of Liverpool has published possible pharmacokinetic interactions of experimental COVID-19 therapies to aid decision making as well. (11).

9. Paediatric Patients

Generally, with a rate of only 1% of overall cases, children and adolescent are far less affected by COVID-19 than adults (9, 78). Compared to adults, children usually show a mild course of the disease and severe cases are rare. So far, the reason for this phenomenon remains unclear. Overall, paediatric patients rarely have to be admitted to a paediatric ICU (PICU) (79). Severe cases of COVID-19 usually affect Infants and toddlers as one-third of patients with COVID-19 admitted to PICU were below 1 year of age. So far, only a few children have died from illness related to COVID-19 and mortality in the paediatric population is extremely low with 0.0018% (79). However, it has to be acknowledged that current data is not robust enough to draw firm conclusions as asymptomatic COVID-19 cases may not have been counted

appropriately. In Germany, so far 22 children with COVID-19 required admission to PICU, and only one case of death has been reported (https://dgpi.de/covid-19-survey-update-kw29/).
A systematic review on 2914 paediatric COVID-19 patients showed that 47% had fever at some point during the disease. Other frequent symptoms included coughing (48%), pharyngitis (29%) and gastrointestinal complaints (10%), e.g. nausea and vomiting or diarrhoea (79). So far, only single cases of COVID-19 pneumonia and acute respiratory failure were reported (80,81).
The same considerations and limitations apply for paediatric patients compared to adults when evaluating therapeutic options like oxygen insufflation, HFNC, non-invasive ventilation and intubation for risks of transmission for personnel and others. Like in the adult population, so far, there has not been a medical treatment with significant effectiveness in paediatric patients with COVID-19; as well, randomised controlled trails are lacking.
There have been several case reports referring to a COVID-19 associated acute hyperinflammatory syndrome in children that involves multiple organs (paediatric inflammatory multisystem syndrome, PIMS) (82-84). Apart from fever, exanthema, conjunctivitis, polyserositis, gastrointestinal symptoms and oedema, those patients often present with vasoplegic shock. Some also show symptoms similar to the Kawasaki syndrome, e.g. coronary involvement and left-ventricular dysfunction (84). In most of the cases, as with the classic Kawasaki syndrome, treatment was complemented with anti-inflammatory steroids (prednisone, prednisolone or methylprednisolone 2mg/kg/d), high dose immunoglobulins (2g/kg) and, in some cases, acetylsalicylic acid (50 mg/kg). Biologicals like the TNF-alpha antagonist infliximab (5mg/kg i.v. over 2 hours, weekly) or the interleukin-1 receptor antagonist Anakinra (2-6 mg/kg BW/d s.c.) can be considered as rescue therapy if other options fail.
Symptoms of vasoplegic shock are treated with fluids and vasopressors. Hyperinflammatory syndromes are usually manageable within the first days of presentation; only a few cases treated with ECMO have been reported. Although causal association of PIMS with COVID-19 is unclear, all cases in Germany are registered by the German Society of Paediatric Infectious Diseases (Deutsche Gesellschaft für Pädiatrische Infektiologie; https://dgpi.de/pims-survey-anleitung/) since May 2020.

10. Ethical Considerations

In general, treatment of the critically ill COVID-19 patient follows the universal ethical principles of autonomy, welfare, do-not-harm, equity and human dignity. Two requirements are mandatory to justify and pursue medical treatment: 1. Beginning and continuing treatment is medically indicated, and, 2. The treatment is in concordance with the patient´s will. If the proposed treatment plan complies with both, it is obligatory to start or continue medical

treatment. If one of the requirements is violated, it is not only permitted but rather demanded to change goals of care and limit treatment options (86).
Recommendations for the treatment of COVID-19 patients should also incorporate palliative care as one aspect of a comprehensive plan. In this regard, decision making against ICU treatment or a change in goals of care need to be respected and followed as well (87).
In the case of an uncontrollable up-surge in critically ill patients in Germany and a factual limitation of ICU resources despite all efforts to utilise maximum available ICU capacity, clinicians may use recently published recommendations for resource allocation in intensive care medicine in the context of the COVID-19 pandemic to guide decision making (88).

11. Management of ICU Capacity

The German *ARDS-Netzwerk* and the division *Respiratory Failure* within the *German Interdisciplinary Association of Critical Care and Emergency Medicine* (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin, DIVI) have launched a website in cooperation with the RKI, the *DIVI intensive care medicine registry* (DIVI-Intensivregister). It provides an overview of ICU bed capacities in Germany. All hospitals with critical care treatment options are required to fill in their occupied and available low-care, high-care and ECMO capacities. On April 8th, 2020, a new federal regulation on maintenance and protection of ICU capacities in Germany took effect (Verordnung zur Aufrechterhaltung und Sicherung intensivmedizinischer Krankenhauskapazitäten (DIVI-Intensivregister-Verordnung), making it mandatory for hospitals to report to the registry on a daily basis. The registry can be accessed at www.intensivregister.de.

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13. Conflicts of interest:

S. Kluge received research support by Ambu, ETView Ltd, Fisher & Paykel, Pfizer and Xenios. He also received lecture honorarium from ArjoHuntleigh, Astellas, Astra, Basilea, C.R.Bard, Baxter, Biotest, CSL Behring, Cytosorbents, Fresenius, Gilead, MSD, Orion, Pfizer, Philips, Sedana, Sorin, Xenios and Zoll. He received consultant honorarium from AMOMED, Astellas, Baxter, Bayer, Fresenius, Gilead, MSD, Pfizer and Xenios. T. Welte received consultant honorarium from MSD, GSK, Boehringer, Immunogenic, Novartis, AstraZeneca and Roche. He received lecture honorarium and travel grants from Gilead and research support by Roche, MSD, Gilead, Immunogenic, Novartis, GSK and CSL Behring (DSMB). S. Weber-Carstens works in a research cooperation with Dräger. B. Salzberger received consultant honorarium from Falk Foundation, GSK, Roche and Sanofi, and, research support by Bosch-Stiftung, GSK and Biochryst. F. Langer received lecture and consultant honorarium as well as research support by Aspen, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Chugai, CSL Behring, Daiichi Sankyo, LEO Pharma, Pfizer, Roche, Sanofi, SOBI and Takeda. M. Westhoff received lecture honorarium from Actelion, Boehringer, Novartis and Löwenstein as well as research support by Bayer.

M. Pfeifer received lecture honorarium from Astra-Zeneca, Boehringer, Chiesi, Glaxo-Smith-Kline, Novartis and Roche. He also received consultant honorarium from Boehringer, Chiesi, Novartis and Roche, and, travel support from Boehringer. B.W. Böttiger received lecture honorarium from Forum für medizinische Fortbildung (FomF), ZOLL and C.R. Bard. G. Marx received consultant honorarium and research support by Biotest, B.Braun und Adrenomed, he also received lecture compensation by B.Braun und Philips. C. Karagiannidis received consultant honorarium from Bayer und Xenios. U. Janssens G. Schälte, P. Gastmeier, M. Wepler und F. Hoffmann declare no conflicts of interest.

For the process of assessment and evaluation of potential conflicts of interest please see AWMF-IMWi webpage and regulations.

Table 1

Interventions to minimise aerosol formation and exposure (adapted from (36); PEEP = positive end-expiratory pressure, CPAP = Continuous Positive Airway Pressure, ASB = Assisted Spontaneous Breathing).

Aerosol formation by	Risk management
Endotracheal intubation	avoid emergency intubation performed by the most experienced physician rapid sequence induction avoid bag mask ventilation optimal preparation and briefing consider video laryngoscopy to increase distance stylet for intubation consider transparent plastic sheet to cover patient's face consider intubation box
Pre-oxygenation	assure tight fitting mask using mask with both hands to hold in place FiO_2 of 1.0 maximum PEEP 5 cmH_2O duration: 3 min of spontaneous breathing or 1 min of 8-12 deep breaths or 1 min CPAP/ASB of 5/15 cmH_2O
Fibre-optic intubation	avoid where possible use local anaesthetics
Suction	use closed systems
Non-invasive ventilation	only when absolutely indicated assure tight fitting mask
High-flow nasal cannula	only when absolutely indicated cover nose and mouth with mask
Bronchoscopy	only when absolutely indicated
Tracheostomy	performed by the most experienced be aware of high level of aerosol formation in any technique consider postponing until patient is tested negative
Disconnection of tube	leave HME filter on tube clamp tube respirator on stand-by during procedure
Extubation	avoid suction and inflation manoeuvres respirator on stand-by during procedure leave HME filter on tube consider transparent plastic sheet to cover patient's face post procedural tight-fitting mask for oxygenation use regular protective face mask when adequate spontaneous breathing

Figure 1

Management and hierarchy of therapeutic options in acute respiratory failure associated with COVID-19 (adapted from (16); NIV = non-invasive Ventilation, PEEP = positive end-expiratory pressure, CPAP = Continuous Positive Airway Pressure).