

**Permanent Working Group of Competence and Treatment Centers for High-consequence Infectious Diseases  
at the Robert Koch Institute**

## **Notes on the identification, diagnosis and treatment of patients with COVID-19**

As of: 16/07/2021

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### **With cooperation from:**

German Society for Pediatric Infectious Diseases (DGPI)

German Society of Infectious Diseases (DGI)

German Respiratory Society (DGP)

Federal Institute for Drugs and Medical Devices (BfArM)

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## Summary of recent amendments

Amendment dated 16/07/2021:

Adjustment of information on monoclonal antibodies, tocilizumab and baricitinib

Amendment dated 28/04/2021:

Addition of note on budesonide; adjustment in the section on monoclonal antibodies

Amendment dated 01/03/2021:

Addition of information on monoclonal antibodies; tocilizumab, addition of note on colchicine

Amendment dated 28/01/2021

Adjustment of the information on monoclonal antibodies, convalescent plasma and interleukin-6 inhibitors

Amendment dated 30/12/2020

Adjustment of antigen detection information

Amendment dated 23/12/2020

Addition of information on monoclonal antibodies, baricitinib, ivermectin; restriction of the authorization of remdesivir

Amendment dated 26/11/2020

Note on the WHO statement on remdesivir

Amendment dated 05/11/2020

Adjustment of note on the use of remdesivir; adjustment of note on corticosteroid therapy in children; addition of information on antigen testing

Amendment dated 09/10/2020

Adjustment of criteria for clinical classification; additional material on anticoagulation, the use of remdesivir and dexamethasone; addition of note regarding children

Amendment dated 06/08/2020

Adjustment of the information on tocilizumab

Amendment dated 22/07/2020

Update of information on dexamethasone; editorial adjustments

Amendment dated 16/07/2020

Additional information on remdesivir; diagram for remdesivir and dexamethasone.

Amendment dated 09/07/2020

Treatment information for remdesivir and dexamethasone

Amendment dated 04/07/2020

Additional information on antiviral therapies (remdesivir)

Amendment dated 02/07/2020

Additional information on antiviral therapies (lopinavir/r)

Amendment dated 24/06/2020

Adjustment of the information on dexamethasone

Amendment dated 18/06/2020  
Additional information on dexamethasone

Amendment dated 10/06/2020  
Additional information on antiviral therapies (convalescent plasma)

Amendment dated 29/05/2020  
Inclusion of warnings against the use of hydroxychloroquine

Amendment dated 19/05/2020  
Notes on the use of remdesivir

Amendment dated 07/05/2020  
Symptom list update and editorial amendments

Amendment dated 17/04/2020  
Individual updates and editorial amendments

Amendment dated 08/04/2020  
Inclusion of notes on thromboembolic events; general notes on antiviral treatment and explanations regarding individual treatment; off-label use; hardship programme.

## Preamble

Our entire healthcare system is facing severe challenges due to the pandemic caused by the betacoronavirus SARS-CoV-2. Evidence-based, medical knowledge on COVID-19, the disease associated with the novel virus, is only becoming available gradually. The contents of this document and the supplementary sources are updated regularly in response to the continuous changes in the evidence base. It is therefore essential that only the most recent version of this document is used.

This document aims to provide guidance on the management of COVID-19 patients and to establish more clarity by bringing together available German documentary sources. Therefore, the majority of used links in this document refer to documents in German only.

For this reason, the German version is also updated in shorter intervals than the English one.

## Infection

Transmission is caused by infected persons, whether symptomatic or asymptomatic. Infection can possibly occur as much as 1–2 days before an infected person becomes symptomatic. Current data indicates that the average duration of infectiousness among immunocompetent persons is approx. 10 days in the case of mild to moderate disease progression. Significantly longer periods of infection have been observed in cases of severe progression and immunocompromised patients.

The primary transmission pathway for SARS-CoV-2 is respiratory ingestion of fluid particles containing the virus (droplets and/or aerosols) that are generated by breathing, coughing, talking and sneezing. Blood, faeces, urine and other bodily fluids are not considered infectious among COVID-19 patients. Transmission through smear infections via contaminated surfaces cannot be ruled out with certainty ([www.rki.de/covid-19-steckbrief](http://www.rki.de/covid-19-steckbrief)).

All potential transmission pathways must be taken into account in everyday clinical routines. Activities associated with an elevated risk of transmission include aerosol-producing procedures such as intubation, bronchoscopy or dental treatments in particular. It follows, therefore, that rigorous implementation of basic hygiene and personal protection measures must be assigned considerable importance ([www.rki.de/covid-19-hygiene](http://www.rki.de/covid-19-hygiene); notes on the handling of personal protective equipment/PPA, [www.rki.de/covid-19-psa](http://www.rki.de/covid-19-psa)).

## Clinical symptoms, course of disease and complications

### Clinical symptoms:

Current insight indicates a mean incubation period of 5–6 days, although up to 14 days is also possible. COVID-19 patients experience nonspecific symptoms that resemble many other respiratory diseases. Mild symptoms such as headaches and a ‘blocked’ nose may occur on their own. A phase with ‘more typical’ symptoms such as fever or coughing may be preceded by a phase of milder symptoms for one or two days. The disease may also run its course without fever ([www.rki.de/covid-19-steckbrief](http://www.rki.de/covid-19-steckbrief)).

The disease usually begins with the following symptoms, either individually or in combination:

- Frequent symptoms/manifestations
  - Coughing, productive and nonproductive

- Fever
  - Runny nose
  - Impairment of the sense of smell and/or taste
  - Pneumonia
- Other possible symptoms  
Sore throat, shortness of breath, headaches, aching limbs, loss of appetite, weight loss, nausea, abdominal pain, vomiting, diarrhoea, conjunctivitis, rash, lymph node swelling, apathy, somnolence

In cases of unconfirmed SARS-CoV-2 infections with relevant symptoms, other infectious and noninfectious differential diagnoses must be taken into account.

**CAVE: Take differential diagnoses into account**

**Course of disease:**

Around 81% of all diseases show a mild to moderate course. During the course of the disease, approximately 14% will typically experience clinical deterioration accompanied by dyspnoea and/or hypoxaemia around 7–10 days after the onset of symptoms. ‘Silent hypoxaemia’ is observed in many of these cases, in which there is subjectively no significant dyspnoea despite a considerable impairment in oxygenation. Treatment on an intensive care unit is indicated for around 14% of hospitalised patients. At present, just over half of the COVID-19 patients in intensive care units in Germany (approx. 57% as per 28/04/2021, [DIVI-Intensivregister](#)) require invasive ventilation. In severe courses involving septic shock and/or multiple organ failure, diagnosis should be carried out and therapy initiated in accordance with the guidelines if a bacterial co-infection is suspected. In Germany, the case fatality rate (CFR) among COVID-19 patients below the age of around 50 is less than 0.1%, rising with increasing age to over 10% among persons over 80. ([www.rki.de/covid-19-steckbrief](http://www.rki.de/covid-19-steckbrief)).

*Clinical classification of COVID-19 infection according to severity (adapted from [WHO Therapeutics and COVID-19: living guideline](#)):*

**Table 1:** Clinical classification of COVID-19 infection (adapted from [WHO Therapeutics and COVID-19: living guideline](#)):

Classification	Definition	Symptoms
Mild disease	No pneumonia	
Moderate disease	Pneumonia	No symptoms of severe pneumonia
Severe disease	Severe pneumonia	defined by fever and bilateral pulmonary infiltrates and either respiratory rate > 30/min, severe respiratory distress or SpO <sub>2</sub> <90–94% in room air
Critical disease	ARDS	

Critical disease	Hyperinflammation	clinical symptoms of sepsis or septic shock with multiple organ failure
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The risk of a severe course of the disease increases with age among persons aged 50 to 60. Various pre-existing conditions, e.g. stem cell or organ transplantation, trisomy 21, obesity with BMI >35, cardio-vascular diseases, diabetes mellitus, chronic lung and liver diseases, chronic kidney diseases including dialysis patients, sickle cell anaemia or thalassaemia and other forms of immunosuppression (e.g. tumour patients, HIV-infected patients with compromised immune systems, iatrogenic immunosuppression), increase the risk of a severe course of disease regardless of age.

In addition to age (>50 years), predictors for a severe course are male sex, dyspnoea and persistent fever, as well as pronounced lymphocytopenia and elevation of biomarkers such as CRP, D-dimer, LDH and troponin. Antipyretics show little ability to modulate fever in many cases.

### Complications and long-term effects

A variety of organ manifestations and complications may occur over the course of the disease. In addition to respiratory insufficiency with pulmonary involvement, impairment of kidney function up to the need for dialysis, impairment of liver function, cardiomyopathies, neurological symptoms and frequent thromboembolic events are frequently observed. Some patients with severe SARS-CoV-2 infection experience deterioration in the form of a hyperinflammatory syndrome approximately 8–15 days after the onset of illness, which may result in multiple organ failure associated with high mortality.

Symptoms may persist for several months among a considerable proportion of patients. Six months after the onset of symptoms, for instance, three quarters of patients report at least one symptom such as fatigue and more than half of the patients still exhibit radiological evidence of lung changes (Huang et al, Lancet January 2021 DOI: [https://doi.org/10.1016/S0140-6736\(20\)32656-8](https://doi.org/10.1016/S0140-6736(20)32656-8)).

#### CAVE

More frequent occurrence of thromboembolic events of different degrees of severity at different times during the disease and also in young patients without risk factors or pre-existing conditions.

Elevated D-dimers or significant increases thereof may indicate thromboembolic complications and are associated with considerably increased mortality.

### Case detection

A flow chart for case detection is available on the RKI website [www.rki.de/covid-19-flussschema](http://www.rki.de/covid-19-flussschema).

### Patient care

Testing for SARS-CoV-2 infection during normal operations in first-aid centres or doctors' surgeries should be avoided and should be carried out in a separate space if possible ([www.rki.de/covid-19-patientenversorgung-ambulant](http://www.rki.de/covid-19-patientenversorgung-ambulant)).

Patient care can be provided within an inpatient and outpatient setting with due adherence to the necessary strict isolation measures, and depending on the clinical manifestation of the disease. The RKI website contains notes on the outpatient ([www.rki.de/covid-19-ambulant](http://www.rki.de/covid-19-ambulant)) and inpatient

([www.rki.de/covid-19-patientenversorgung](http://www.rki.de/covid-19-patientenversorgung)) management of COVID-19 patients, as well as notes on necessary protective policies depending on the measures that will be performed on the patient ([www.rki.de/covid-19-hygiene](http://www.rki.de/covid-19-hygiene)).

### Outpatient care

The isolation of infected persons from non-infected persons must be guaranteed in outpatient care settings. Moreover, regular clinical follow-up is essential to detect clinical predictors of a severe course (e.g. persistence or increase of fever or dyspnoea) requiring hospitalisation of the patient. Patients with risk factors for a severe course should be closely monitored in particular and, if necessary, admitted to inpatient care at an early stage ([www.rki.de/covid-19-ambulant](http://www.rki.de/covid-19-ambulant)). An evaluation of these patients for potential administration of monoclonal antibody treatment might be useful. The STAKOB Infectious Diseases Advisory Network centres and the DGI are available to provide guidance ([www.rki.de/stakob-ibn](http://www.rki.de/stakob-ibn)).

#### CAVE in outpatient care settings:

Monitoring of clinical symptoms is mandatory, especially after 7–10 days; further diagnosis and, if necessary, hospitalisation if clinical symptoms deteriorate or do not improve, especially if fever or dyspnoea persist or increase.

Repeat review of infectious and noninfectious differential diagnoses if the symptoms persist.

Assess the patient with regard to the possible administration of monoclonal antibodies

### Inpatient care

Patients should be placed in cohorts during inpatient care. SARS-CoV-2-positive patients and SARS-CoV-2-negative patients must be placed in separate cohorts in order to prevent nosocomial transmission. Where necessary, entire hospitals can be designated for the care of COVID-19 patients. Hospitals that also care for non-COVID-19 patients should have areas where suspected cases are placed in a cohort and treated separately from regular hospital operations until a conclusive diagnosis is available (for more information, visit [www.rki.de/covid-19-patientenversorgung](http://www.rki.de/covid-19-patientenversorgung)).

### Diagnosis

The diagnoses referred to here apply in particular to patients over the course of their inpatient treatment. Depending on the clinical symptoms, additional differential diagnoses (e.g. influenza, other respiratory viruses, bacterial infections) should be taken into consideration in addition to the diagnosis of SARS-CoV-2 infection. For additional notes on the testing of patients for SARS-CoV-2 infection, refer to the RKI website at ([www.rki.de/covid-19-diagnostik](http://www.rki.de/covid-19-diagnostik))

### PCR diagnosis:

Direct detection of SARS-CoV-2 can be obtained by PCR from a deep oro-/nasopharyngeal swab or sputum (induced where necessary with suitable training and adherence to the protective measures). Where SARS-CoV-2 infection is suspected, samples should be taken simultaneously from the upper and lower airways if possible, depending on the clinical situation. Correct collection of the swab samples is crucial for the quality of the results.

A second sample should be tested if there is an urgent clinical suspicion of infection, despite a negative result. In patients in the later course of the disease (pneumonia, ARDS), the smear from the upper airway may already be negative for SARS-CoV-2 in the specific PCR test, although viral RNA remains detectable in the lower airway. Sputum production can be induced in these cases (by inhalation with a 3% NaCl solution) in order to avoid exposing the patient to the additional risks of a bronchoscopy merely to obtain tracheobronchial secretions for diagnostic purposes. The process of obtaining induced sputum causes aerosol formation and must therefore only take place with special precautionary measures. If the collection of respiratory materials is not possible despite several attempts, a stool sample for PCR examination can also be helpful for diagnosis in some cases (up to 50% of patients with SARS-CoV-2 infection also excrete the virus in their faeces). In cases of strong clinical suspicion, negative test results do not constitute a clear exclusion of diagnosis.

### **Antigen detection:**

SARS-CoV-2 rapid antigen tests are increasingly being offered. Antigen (AG) tests are based on the detection of viral protein in respiratory materials. Provided defined requirements are met, AG tests can be a useful addition to PCR tests if an initial (preliminary) decision on the possible presence of a potentially transmissible infection needs to be made quickly (on-site, POCT) during the early phase of infection. Nonetheless, a negative AG test does not exclude the possibility of SARS-CoV-2 infection. The use of AG tests is also included in the [National Testing Strategy](#) as a means of ensuring efficient deployment of test capacities for the diagnosis of SARS-CoV-2 infections.

At present, independent validation of the AG test performance parameters takes place at several centres that make their findings publicly available (see [Foundation for Innovative Diagnostics](#) (FINDDx)). For more detailed information, visit [www.rki.de/covid-19-diagnostik](http://www.rki.de/covid-19-diagnostik). Lists of the SARS-CoV-2 rapid AG rapid tests that, according to the manufacturer, satisfy all the [Minimum Criteria for AG Tests](#) defined by the Federal Institute for Vaccines and Biomedicines (PEI) in coordination with the Robert Koch Institute (RKI) is found on the Federal Institute for Drugs and Medical Devices (BfArM) website:

[List of antigen tests for direct detection of the SARS-CoV-2 coronavirus pathogen](#)

[https://www.bfarm.de/DE/Medizinprodukte/Aufgaben/Spezialthemen/Antigentests/\\_node.html](https://www.bfarm.de/DE/Medizinprodukte/Aufgaben/Spezialthemen/Antigentests/_node.html)

In addition, the PEI conducts a comparative evaluation of AG test sensitivity in the laboratory:

[www.pei.de/SharedDocs/Downloads/DE/newsroom/dossiers/evaluierung-sensitivitaet-sars-cov-2-antigentests-04-12-2020.pdf](http://www.pei.de/SharedDocs/Downloads/DE/newsroom/dossiers/evaluierung-sensitivitaet-sars-cov-2-antigentests-04-12-2020.pdf)

### **Serological diagnosis:**

Serological test options are irrelevant to the diagnosis of acute infection, but may be useful to obtain additional information in the later course of the disease. Further trials are required to investigate their usefulness, e.g. in regard to epidemiological issues as well. At present, these tests also do not have adequate precision to clarify the question of existing immunity (without known previous experience of disease).

**Frequent laboratory findings:**

Leukocytopenia with lymphocytopenia and thrombocytopenia as well as elevated CRP, transaminase and LDH are common. An increase in procalcitonin – which is potentially indicative of bacterial infection – is observed less frequently and in these cases only to a slight degree. Elevated troponin is frequent in severe courses and requires aetiological clarification. High troponin values (>5 times above the reference range) in particular are associated with a poor prognosis. Persistently high or increasingly elevated D-dimers are indicative of coagulation activation in the context of immunological dysregulation and may point to a relevant risk of thromboembolic events or pre-existing thromboembolic complications. Cut-off values for D-dimers proposed in the relevant literature in these circumstances (e.g. initiation of intensified anticoagulation) are >1000–1500 ng/ml.

**Sample material:**

1. For the diagnosis of SARS-CoV-2 ([www.rki.de/covid-19-diagnostik](http://www.rki.de/covid-19-diagnostik)):
  - Detection of the pathogen by means of PCR, if necessary by means of AG test, from deep oro-/nasopharyngeal swab, (if necessary induced) sputum and/or tracheobronchial secretions, if necessary repeat in case of negative result and persistent suspicion (see above), if necessary also diagnosis based on a stool sample.  
CAVE: Aerosol generation
  - For an example video on the correct procedure for taking a swab, watch: '[How to Obtain a Nasopharyngeal Swab Specimen](#)' (N Engl J Med 2020; 382:e76, DOI: 10.1056/NEJMvcm2010260)
  - Serological test methods are only meaningful after 7–10 days at the earliest
2. To perform bacteriological testing for differential diagnoses:
  - Collection of several blood cultures (aerobic + anaerobic in each case) for pathogens + resistance
  - Sputum, Bronchoalveolar lavage (BAL), tracheobronchial secretion for pathogens + resistance
  - Urine diagnosis for pneumococci, legionella
3. Other diagnostic procedures:
  - Regular blood sampling with differential blood count, clinical chemistry depending on the course of the disease with control of CRP, LDH, kidney and liver function parameters, electrolytes, and, depending on the course of the disease, procalcitonin, troponin, D-dimer, IL-6

**Imaging:**

Changes are visible in a standard X-ray image of the thorax among 50–60% of the examined persons. In CT examinations of the lung, changes are found in approx. 85% of cases in the form of ground-glass opacities, bilateral or more rarely unilateral and often peripherally localised compressions and/or interstitial proliferation of bright opacities.

**Treatment**

Treatment depends on the severity of the disease, whereby supportive measures are of considerable importance in each type of disease progression. If there is an increase in dyspnoea, increased hypoxaemia and persistence of fever, the possible development of a critical progression should be considered and early intensive medical monitoring and care initiated.

In addition, clinical indications of possible thromboembolic events (e.g. DVT, PE) should be taken into account in order to initiate early diagnosis and treatment if necessary.

### General measures during inpatient treatment:

- Restrictive fluid therapy (as this can worsen oxygenation), nutritional optimisation
- Close monitoring of vital parameters to detect clinical deterioration at an early stage
- Resolute initiation of thrombosis prophylaxis, therapeutic anticoagulation if necessary, taking into account the potential risk of bleeding
- Consideration of comorbidities
- Oxygen administration as needed (nasal, via mask, if necessary nasal 'high-flow' oxygen therapy), target SpO<sub>2</sub> > 90% in non-pregnant adults, > 92 - 95% in pregnant women, > 88% in COPD patients. ([S3 Guideline – 'Recommendations on Inpatient Treatment of Patients with COVID-19'](https://www.awmf.org/leitlinien/detail/II/113-001LG.html) <https://www.awmf.org/leitlinien/detail/II/113-001LG.html>, [www.who.int/publications-detail/clinical-management-of-covid-19](http://www.who.int/publications-detail/clinical-management-of-covid-19))
- CAVE: Possible aerosol formation in case of high oxygen flow
- Regular control of inflammation parameters (CRP, IL-6), kidney and liver function, coagulation (incl. D-dimer)
- Imaging, depending on the clinical course
- Take co-infections/secondary infections into account
- Collection of several blood culture sets if necessary
- Respiratory materials depending on the clinical course (pathogens + resistance, SARS-CoV-2 PCR, respiratory viruses, HSV)

The following points must be reevaluated on a regular basis during the treatment of patients with severe and critical courses:

- Early administration of oxygen, if possible already place awake patients in prone position ('awake proning'), if necessary nasal 'high-flow' oxygen therapy, non-invasive or invasive ventilation
- ECMO if necessary, early establishment of contact with the regional ECMO centre to obtain advice on complex ventilation situations
- Early detection and treatment of potential complications, in particular indications of thromboembolism as well
- Prevention of secondary infections
- Sepsis treatment according to the current German S3 Guideline on [Prevention, Diagnosis, Treatment and Follow-up Care of Sepsis](#)

### Supplementary guidelines and treatment recommendations:

- [S3 Guideline – 'Recommendations on Inpatient Treatment of Patients with COVID-19'](https://www.awmf.org/leitlinien/detail/II/113-001LG.html), <https://www.awmf.org/leitlinien/detail/II/113-001LG.html> German Society of Medical Intensive Care and Emergency Medicine (DGIIN), German Interdisciplinary Association of Intensive and Emergency Medicine (DIVI), German Respiratory Society (DGP), AWMF Register No. 113/001
- A summary of guidelines by other professional associations is available on the AWMF web pages: <https://www.awmf.org/die-awmf/awmf-aktuell/aktuelle-leitlinien-und-informationen-zu-covid-19/covid-19-leitlinien.html>
- Guidance on the clinical management of patients with COVID-19, WHO: <https://www.who.int/publications-detail/clinical-management-of-covid-19>
- Statement by DGPI, GPP, API, GKJR, DGPK and STAKOB on the clinical presentation and medicinal treatment of children with COVID-19 – Update 11/2020 <https://dgpi.de/stellungnahme-medikamentoesen-behandlung-kindern-covid-19/>

## Medicinal therapies during inpatient treatment:

### **Anticoagulation:**

Data on the management of hypercoagulability for the prevention and treatment of thromboembolic events are not yet consistent. In a retrospective analysis, reduced mortality was shown for both prophylactic and therapeutic anticoagulation (Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study, DOI <https://doi.org/10.1016/j.jacc.2020.08.041>).

From the authors' point of view, initiation of at least prophylactic anticoagulation is therefore indicated upon hospital admission. Intensified anticoagulation appears purposeful for the treatment of critically ill patients. This might consist of a semi-therapeutic LWMH dose or therapeutic anticoagulation (provided patient is not undergoing thromboembolism or ECMO therapy and therapeutic anticoagulation is therefore indicated anyway), depending on the severity of the disease and possibly the increase in D-dimers.

### **Antiviral therapy with remdesivir:**

#### *Background:*

The European Commission granted conditional marketing authorisation for remdesivir (Veklury®) on 3 July 2020. This EU authorisation is essentially based on a trial with about 1000 patients in which remdesivir was shown to reduce the time before symptoms improved among hospitalised patients with supplementary oxygen requirements.

For more information, visit the European Medicines Agency (EMA) website:

[www.ema.europa.eu/en/medicines/human/EPAR/veklury](http://www.ema.europa.eu/en/medicines/human/EPAR/veklury)

Conditional marketing authorisation may be granted to medicinal products:

- that are intended for treating, preventing or diagnosing seriously debilitating or life-threatening diseases
- whose use is also intended for a public health emergency
- are intended for use as orphan medicines

Conditions are imposed on this form of marketing authorisation. For example, the marketing authorisation holder must initiate or complete certain trials to demonstrate that the risk-benefit balance is positive and to answer outstanding questions about the quality, safety and effectiveness of the medicinal product (for more information, visit the Federal Institute for Drugs and Medical Devices page on '[Conditional marketing authorization](#)').

On 20 November 2020, the WHO published a guideline ([Therapeutics and COVID-19: living guideline](#)) with a conditional recommendation against the use of remdesivir, regardless of the clinical stage of the COVID-19 disease. This recommendation is largely based on the findings of the SOLIDARITY trial and a meta-analysis of data from all controlled trials. The findings did not show that remdesivir has any positive effect on mortality. Results from subgroups are not included in this regard or are inadequately available from controlled trials. Following evaluation by the EMA of the final mortality data from the NIAID-ACTT1-study, a restriction of indication for remdesivir was issued on 10 December 2020 (<https://www.ema.europa.eu/en/medicines/human/EPAR/veklury>).

Remdesivir is available in selected pharmacies in Germany as part of an initiative of the Federal Ministry of Health and the European Commission. A list of pharmacies that stock remdesivir as well as a process description for obtaining the medicinal product are available on the RKI website ([www.rki.de/covid-19-arzneimittelbevorratung](http://www.rki.de/covid-19-arzneimittelbevorratung)).

#### *Administration of remdesivir:*

Remdesivir is authorised for the treatment of COVID-19 in adults and adolescents (aged 12 years or older and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen therapy or non-invasive ventilation).

**Table 2:** Overview of possible indications and restrictions on treatment with remdesivir

	Indication (all criteria satisfied)	Not recommended <sup>4</sup>	Contraindications <sup>4</sup>
Adults and adolescents (> 12 years) weighing at least 40 kg <sup>1</sup>	<ul style="list-style-type: none"> <li>- COVID-19 pneumonia</li> <li>- Oxygenation dependency</li> <li>- Duration of symptoms &lt;7 days<sup>2</sup></li> <li>- Positive SARS-CoV-2 PCR within the last 48 h</li> </ul>	<ul style="list-style-type: none"> <li>- Patients without oxygen requirement <b>CAVE: RR &gt; 30/min<sup>3</sup></b></li> <li>- Patients receiving invasive ventilation</li> <li>- Liver dysfunction (GPT ≥ 5x ULN or GPT increase + signs of hepatitis or simultaneous increase in bilirubin, AP or INR).</li> </ul>	<ul style="list-style-type: none"> <li>- Renal insufficiency (GFR &lt; 30ml/min)</li> <li>- Hypersensitivity to the active substance or to any of the excipients</li> </ul>

<sup>1</sup> Refer to the Summary of Product Characteristics, information in German on the EMA website: [www.ema.europa.eu/documents/product-information/veklury-epar-product-information\\_de.pdf](http://www.ema.europa.eu/documents/product-information/veklury-epar-product-information_de.pdf)

<sup>2</sup> The recommended start is within the first 7 days after symptom onset, in exceptional cases up to 10 days, after consultation on infectious diseases, e.g. via the STAKOB Infectious Diseases Advisory Network in cooperation with the German Society of Infectious Diseases ([www.rki.de/stakob-ibn](http://www.rki.de/stakob-ibn)).

<sup>3</sup> Patients with RR >30/min may still be dependent on oxygenation despite their SpO<sub>2</sub> being adequate

<sup>4</sup> A consultation on infectious diseases from the STAKOB Infectious Diseases Advisory Network in cooperation with the German Society of Infectious Diseases must take place beforehand in the event that treatment is under consideration ([www.rki.de/stakob-ibn](http://www.rki.de/stakob-ibn))

It is essential to consider very carefully whether treatment is indicated. **Treatment should be initiated as early as possible** in cases of COVID-19 pneumonia with oxygen dependency. It is recommended that treatment be started **within the first 7 days after symptom onset**. If later initiation of therapy is under consideration, in exceptional cases up to 10 days after the onset of symptoms, a consultation on infectious diseases must take place beforehand without fail, e.g. via the STAKOB Infectious Diseases Advisory Network in cooperation with the German Society of Infectious Diseases ([www.rki.de/stakob-ibn](http://www.rki.de/stakob-ibn)). No benefit was shown among patients receiving non-invasive or invasive ventilation treatment, including ECMO (refer to Figure 1 below).

#### *Dosage recommendations for remdesivir and contraindications:*

The information compiled here in an abbreviated form cannot replace strict compliance with the Summary of Product Characteristics. Information on remdesivir (Veklury®) is also available in German on the EMA website:

[www.ema.europa.eu/documents/product-information/veklury-epar-product-information\\_de.pdf](http://www.ema.europa.eu/documents/product-information/veklury-epar-product-information_de.pdf)

**Table 3:** Overview of dosage recommendations for remdesivir

Patient category	Treatment with remdesivir

<p>Adults and adolescents (&gt; 12 years) weighing at least 40 kg<sup>1,2,3,4,6</sup></p>	<p><u>Day 1</u>: Intravenous loading dose of 200 mg remdesivir as a single dose  <u>From day 2</u>: 100 mg remdesivir, administered intravenously as a single dose  Treatment usually lasts 5 days  Treatment can be extended to max. 10 days, but prior consultation on infectious diseases is urgently recommended<sup>1</sup>.</p>
<p>Children (up to 12 years)<sup>3,4</sup></p>	<p>No data are available concerning the safety and effectiveness of remdesivir treatment on children under 12 years and with a body weight &lt;40 kg. No marketing authorisation has been issued for this group. A statement by the German Society for Pediatric Infectious Diseases (<a href="https://dgpi.de/stellungnahme-medikamentoesen-behandlung-kindern-covid-19/">https://dgpi.de/stellungnahme-medikamentoesen-behandlung-kindern-covid-19/</a>) and the American association PIDS provides dosage recommendations for children below the age of 12. They are based on experience from the use of remdesivir for the treatment of Ebola Virus Disease.</p>
<p>Pregnant women and nursing mothers<sup>3,4,5</sup></p>	<p>Pregnancy: In the absence of meaningful data on humans or animals: Should only be administered to pregnant women when absolutely necessary.  Nursing: Remdesivir has been shown to pass into breast milk in animal models. Nursing should therefore be discontinued for the duration of treatment with remdesivir.</p>

<sup>1</sup>Consultation on infectious diseases is available at any time, e.g. via the STAKOB Infectious Diseases Advisory Network in cooperation with the German Society of Infectious Diseases ([www.rki.de/stakob-ibn](http://www.rki.de/stakob-ibn))

<sup>2</sup>No dose adjustment is necessary for patients aged 65 and older.

<sup>3</sup>The pharmacokinetics of remdesivir in patients with impaired kidney function are unknown. Patients with a GFR <30ml/min should not be treated with remdesivir.

<sup>4</sup>The pharmacokinetics of remdesivir in patients with impaired liver function are unknown. It is not known whether dose adjustment is necessary for these patients. Administration should therefore only take place after a strict review of the indication.

<sup>5</sup>At present, experience available concerning the administration of remdesivir to pregnant women is non-existent or only very limited. There is not an adequate number of animal trials available with regard to reproductive toxicity. Veklury® must not be used during pregnancy unless the woman's clinical condition necessitates treatment with remdesivir.

<sup>6</sup>Women of childbearing age must maintain effective contraception.

#### *Warnings and precautions for the administration of remdesivir:*

- Daily monitoring of liver function parameters and **decision against or interruption of treatment with remdesivir if the following laboratory values are obtained:**
  - o Baseline or increase in ALT  $\geq 5$  times the normal upper limit (resumption of remdesivir therapy may be possible if ALT returns to < 5 times the normal upper limit).
- OR
- o Rise in ALT combined with indications of hepatitis or concomitant rise in bilirubin, AP or INR
- Daily monitoring of kidney function parameters and **no treatment with remdesivir if GFR < 30ml/min**; also because of the excipient Betadex sulphobutyl ether sodium, which is excreted via the kidneys and has nephrotoxic potential. At present, few data are available concerning use on patients requiring dialysis; if necessary, this should be

evaluated in individual cases by means of TDM.

- Hypersensitivity reactions (including infusion-related reactions) and anaphylactic reactions; reduction of the infusion rate up to a maximum infusion duration of 120 min; interruption of treatment with remdesivir in case of clinically relevant hypersensitivity reaction.
- **No concomitant use with chloroquine or hydroxychloroquine** due to the potentially antagonistic effects of these substances on the antiviral effectiveness of remdesivir.
- The use of strong inducers of P-gp (e.g. rifampicin) that may lower the plasma concentrations of remdesivir is not recommended.

*Contraindications for the use of remdesivir:*

- Hypersensitivity to the active substance or one of the excipients (e.g. Betadex sulphobutyl ether sodium).

*Side effects with the use of remdesivir:*

The following table contains an overview of the known side effects that may occur during administration of remdesivir:

**Table 4:** Overview of remdesivir side effects\*

Side effect	Frequency
Elevated transaminase levels	Very common ( $\geq 1/10$ )
Headaches	Common ( $\geq 1/100$ to $< 1/10$ )
Nausea	Common ( $\geq 1/100$ to $< 1/10$ )
Exanthema	Common ( $\geq 1/100$ to $< 1/10$ )
Hypersensitivity	Rare ( $\geq 1/10.000$ bis $< 1/1.000$ )
Infusion-related reactions	Rare ( $\geq 1/10.000$ bis $< 1/1.000$ )

\*[www.ema.europa.eu/documents/product-information/veklury-epar-product-information\\_de.pdf](http://www.ema.europa.eu/documents/product-information/veklury-epar-product-information_de.pdf)

***Immunomodulatory treatment with corticosteroids:***

***Background:***

Routine corticosteroid administration is not recommended without clear indication. Data evaluation of the dexamethasone treatment arm in the RECOVERY Study indicated that dexamethasone treatment led to an overall reduction in 28-day mortality in comparison to 'usual care' (NEJM 2021, Dexamethasone in Hospitalized Patients with Covid-19, [www.nejm.org/doi/10.1056/NEJMoa2021436](http://www.nejm.org/doi/10.1056/NEJMoa2021436)). This effect was most pronounced in the group of patients undergoing invasive ventilation and with a disease duration of more than 7 days upon inclusion. The effect was less pronounced in the group of patients receiving oxygen therapy or non-invasive ventilation, but a significant reduction in mortality was also shown in this case. There was no apparent benefit in the group of patients without oxygen therapy. The evaluations even indicate an adverse effect with an increase in mortality, so that dexamethasone is not recommended for patients without oxygen requirements.

Children and adolescents were strongly underrepresented in the trials so far, meaning that an evidence-based recommendation is not possible.

*Indication for the use of dexamethasone:*

After reviewing the available data, the EMA endorses the administration of dexamethasone in adults and adolescents (aged 12 years and over and weighing at least 40 kg) who require supplementary oxygen therapy.

**Table 5:** Indication for the use of dexamethasone

Classification	Definition	Use of corticosteroids
Mild disease	No pneumonia	Not indicated
Moderate disease Pneumonia	No symptoms of severe pneumonia	Not indicated
Severe disease Severe pneumonia	Respiratory rate > 30/min, clinical signs of severe shortness of breath or SpO <sub>2</sub> <90-94 % in room air. <b>PLUS</b> Need for respiratory support or the administration of oxygen <b>PLUS</b> Disease duration of at least 7 days <sup>1</sup>	Treatment is indicated after consideration of the overall clinical disease symptoms and pre-existing conditions
Critical disease ARDS	Need for respiratory support	Indicated
Critical disease Hyperinflammation	Clinical symptoms of sepsis or septic shock with multiple organ failure	Indicated
<sup>1</sup> Use of corticosteroids possible, especially in critically ill patients, even if no exact duration of illness of more than 7 days can be determined <a href="#">Therapeutics and COVID-19: living guideline</a> <a href="https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation">EMA evaluation procedure: https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation</a>		

Based on these data and the other trials published in the meantime, the authors consider treatment with corticosteroids to be indicated in patients with severe or critical SARS-CoV-2 infection (ventilation or oxygen therapy). Whether the start of corticosteroid administration may be purposeful less than 7 days after the onset of the disease is the subject of intense discussion. In line with WHO recommendations, the authors endorse the use of corticosteroids, especially in critically ill patients, even if no exact duration of illness can be determined. Based on the available data, the authors do not believe that corticosteroid treatment is indicated for patients who are not receiving respiratory support.

**Table 6:** Overview of recommended dosages for corticosteroids

Patient category	Treatment with corticosteroids
Adults <sup>1,7</sup>	Dexamethasone 6 mg/day per os or intravenously for max. 10 days <sup>3</sup> Hydrocortisone 50 mg intravenously every 8 hours for 7 to max. 10 days <sup>4</sup>
Children and adolescents below the age of 18 <sup>1,2</sup>	Dexamethasone <sup>6</sup> 0.2–0.4 mg/kg body weight (max. daily dose: 6 mg) once daily intravenously or per os (for 7 to max. 10 days <sup>4</sup> ) or Methylprednisolone <sup>6</sup> intravenously 1–2 mg/kg body weight (max. daily dose: 80 mg) for 3 days, then reduction or Hydrocortisone as applicable <sup>5</sup>
Pregnant women, Nursing women <sup>1</sup>	Prednisolone 40 mg/day per os or hydrocortisone 80 mg BID intravenously for max. 10 days <sup>3</sup>

<sup>1</sup> No specific indication for COVID-19 in the marketing authorisation, but marketing authorisation of dexamethasone and prednisolone for 'severe infectious diseases with toxic conditions'.  
<sup>2</sup> Inclusion of children and adolescents < 18 years in the trial possible from 9 May 2020  
<sup>3</sup> Dose used in the RECOVERY trial  
[www.recoverytrial.net/results/study-protocol-archive](http://www.recoverytrial.net/results/study-protocol-archive)  
<sup>4</sup> WHO guidance specifies the use of dexamethasone or hydrocortisone, [Therapeutics and COVID-19: living guideline](#).  
<sup>5</sup> The effect of this recommendation on seriously ill children and adolescents is not proven, as they were underrepresented or not represented in the existing trials; stating a recommended dose is therefore not possible.  
<sup>6</sup> Dosage applies to paediatric hyperinflammation syndrome (PIMS/MIS-C, see below).  
<sup>7</sup> A single daily dose of steroid (dexamethasone or methylprednisolone) may increase adherence. The dose of 6 mg dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (e.g. 50 mg every 8 hours), 40 mg of prednisone or 32 mg of methylprednisolone (e.g. 8 mg every 6 hours or 16 mg every 12 hours). Monitoring of the blood sugar level is recommended for patients with severe or critical COVID-19.

A current meta-analysis of several trials, including some published in JAMA at the same time, on the administration of corticosteroids confirmed the effects on patients with severe or critical COVID-19. ([jamanetwork.com/journals/jama/fullarticle/2770279](http://jamanetwork.com/journals/jama/fullarticle/2770279))

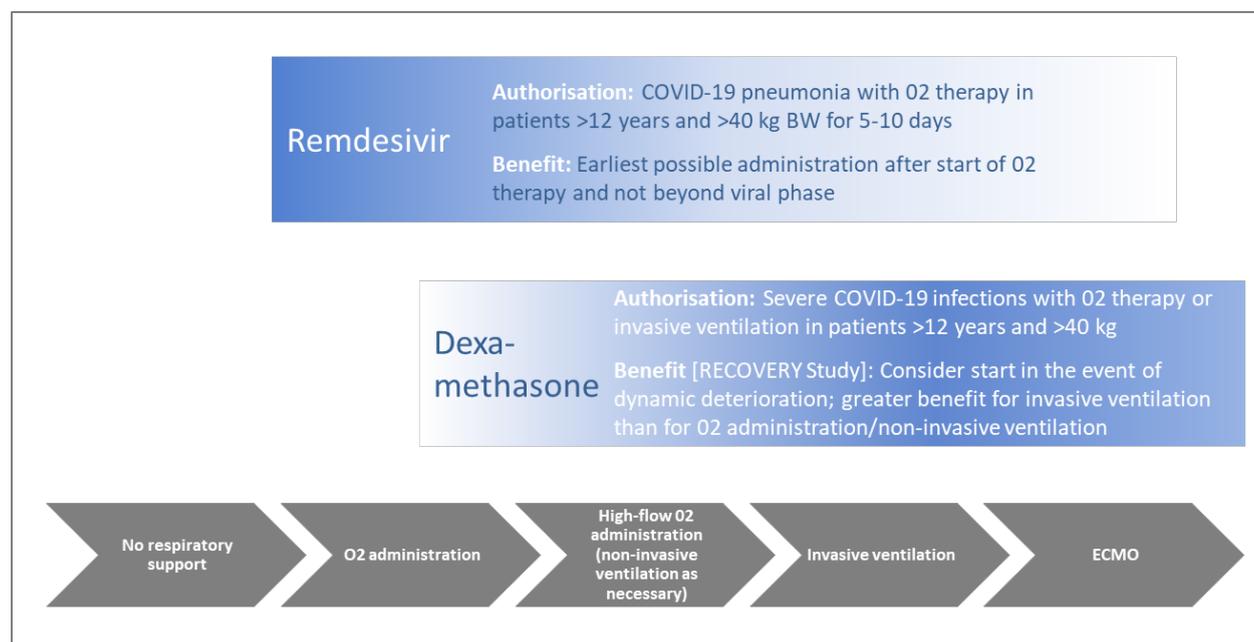
#### *Concomitant administration with remdesivir*

Dexamethasone is considered a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after several administrations. The Summary of Product Characteristics for Veklury® (remdesivir) states that it is improbable that dexamethasone will exhibit a clinically significant effect on remdesivir due to the short period of treatment with remdesivir in cases of COVID-19 and its moderate to high hepatic extraction ratio. It is unknown whether concomitant administration of both substances influences viral clearance.

The following diagram also shows a possible use of remdesivir and dexamethasone over the course of the disease in relation to respiratory support. The information in the text, and also the

relevant summary of product characteristics, must be adhered to on all accounts with regard to the exact indication, warnings and limitations of the evidence base.

**Figure 1:** Administration of remdesivir and dexamethasone in temporal relation to respiratory support



### **Information on clinical trials**

For more information about the clinical trials approved by the Federal Institute for Drugs and Medical Devices and Federal Institute for Vaccines and Biomedicines, refer to the European [Clinical Trials Register](https://www.clinicaltrialsregister.eu/) <https://www.clinicaltrialsregister.eu/> and the German Center for Infection Research website <https://dzif.clinicalsite.org/de/cat/2084>. The Cochrane research network provides an international overview at <https://covid-nma.com/dataviz/>.

### **Individual attempts at treatment**

Section 34 of the German Criminal Code ('necessity as justification') and the doctor's therapeutic freedom can justify individual attempts at treatment. This refers to the use of a medicinal product that is subject to marketing authorisation but has not yet been authorised (or has only been authorised outside Germany) in individual cases and with the consent of the patient concerned, if all other therapeutic options have been exhausted and the attending physician suspects a benefit for the patient based on scientific findings. The focus in this case is on healing the individual patient and not on the systematic acquisition of insight as would be the case in a research trial. Responsibility for administration rests with the attending physician, which necessitates that they exercise a significantly higher standard of due caution.

### **Off-label use**

In addition to individual attempts at treatment with substances that have not yet been approved and are usually only available in small quantities, drugs that have been approved for other diseases are also used in treatment trials for COVID-19 patients. This approach takes place within the framework of 'off-label use', which means that the medicinal products are, in principle, authorised in Germany and hence eligible for marketing under German pharmaceutical laws, but are not administered for the authorised indication, to the authorised population and/or in the authorised dosage. In such cases, the physician is advised to use a more extensive informed consent documentation procedure, which also includes information for the patient about the

nature of such treatment, in particular the fact that the medicinal product is not authorised for the treatment of COVID-19 and that established data on the effectiveness and safety of this off-label use are not available.

### *Recommendations for the attending physician*

Attending physicians are advised to apply the following procedure in cases of individual attempts at treatment or off-label use:

- a regular review of equivalent alternatives if authorised medicines or other therapeutic methods suitable for treatment are or become available, or if such options have not yet been exhausted;
- a particularly careful explanation to the patient or the patient's legal representative of known or suspected side effects with reference to currently unknown risks and possibilities of adverse effects, documented in writing (analogous to the written declaration of informed consent obtained from trial patients according to Sec. 40 et seqq. Medicinal Products Act (AMG));
- obtaining informed consent from the patient or their legal representative;
- a regular and active, systematic search, conducted at short intervals, for information on risks and adverse effects of the medicinal product, ideally also with written documentation, with immediate disclosure to the patient if such risks and adverse effects are found;
- careful and continuous consideration of the risk-benefit ratio for the patient, especially if new complaints are noted;
- detailed documentation in the patient's file including the medicinal product used and its active substance, the treatment plan, the dosage, the incidence of adverse effects and the clinical course of treatment.

Retrieved from:

1. [Treatment with medicines that are not yet authorised](#) (last retrieved on 28/04/2021)
2. [Treatment with as yet unauthorised medicines: Between hope and liability](#) (last retrieved on 28/04/2021)

### *Hardship programmes for medicinal products*

Subject to certain conditions, medicinal products that have not yet been authorised can be dispensed to seriously ill patients within the framework of hardship programmes. Hardship programmes are published by the supreme federal authorities (e.g.

<http://www.bfarm.de/haertefallprogramme>).

### *Incidence of side effects and interactions*

Although long-standing experience concerning the safety of some of these medicinal products still being tested is available based on the indications for which they are approved, previously unknown adverse effects may occur in connection with their use for the treatment of COVID-19. These must be reported on all accounts to the pharmaceutical company, the Drug Commission of the German Medical Association and the competent supreme federal authority: the Federal Institute for Drugs and Medical Devices or the Federal Institute for Vaccines and Medicines (<https://humanweb.pei.de/>).

Drug interactions associated with the different antiviral medicines can be viewed via the following link: <https://www.covid19-druginteractions.org/>.

### *Documentation of the clinical data*

Due to the currently very limited data situation, documentation of the patients' clinical data is recommended when medicinal products that have not yet been authorised are used for the treatment of COVID-19. A variety of databases and trials are available (e.g. [LEOSS.net](http://LEOSS.net), [www.CAPNETZ.de](http://www.CAPNETZ.de), <https://studycenter.charite.de/corona/>, [WHO/ISARIC](http://WHO/ISARIC)).

**Other medicinal products that are currently under investigation:**

At present, remdesivir is the only antiviral drug to have received marketing authorisation for the treatment of COVID-19 (see above). In regard to all other antiviral drugs, the authors of these treatment notes unanimously concur that COVID-19 patients should preferably be treated in the context of clinical trials. Where this is not possible, the attending physician, after very careful individual assessment of the risk-benefit ratio, may consider an individual attempt at treatment or off-label use on a case-by-case basis for the treatment of severe courses or patients with an increased risk of a severe course. If there is any doubt, the attending physician should contact the nearest university hospital, infectious disease centre or STAKOB centre to discuss the specific case and to obtain advice on other possible treatment options. The Infectious Diseases Advisory Network is available to provide consultation and discuss the case in cooperation with the DGI centres. The contact details can be obtained at [www.rki.de/stakob-ibn](http://www.rki.de/stakob-ibn).

*SARS-CoV-2 neutralising monoclonal antibodies (bamlanivimab +/- etesevimab, Casirivimab + imdevimab)*

*Monoclonal antibodies (bamlanivimab, casirivimab plus imdevimab)*

Background:

SARS-CoV-2 neutralising antibodies have a direct antiviral effect and should therefore be used soon after infection with the aim of achieving 'virus neutralisation'. At present, various monoclonal antibodies are under investigation in clinical trials.

A randomised placebo-controlled phase 2 trial of patients at high risk of a severe course or COVID-19-associated symptoms demonstrated a reduction in hospital admissions and emergency department presentations  $\leq 7$  days in the secondary endpoint for the treatment with bamlanivimab (interim analysis of the phase II trial BLAZE-1, Chen et al, DOI: [10.1056/NEJMoa2029849](https://doi.org/10.1056/NEJMoa2029849)), the combination of bamlanivimab plus etesevimab (BLAZE, Gottlieb RL, Nirula A, Chen P et al, JAMA 2021 Jan 21. DOI: [10.1001/jama.2021.0202](https://doi.org/10.1001/jama.2021.0202)) and for the combination of casirivimab plus imdevimab (phase 1/2 trial COV-2067). Patients who are SARS-CoV-2-seronegative and/or have a high viral load benefited most from the treatment (in terms of viral load reduction, REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with COVID-19, Weinreich DM et al. DOI: [10.1056/NEJMoa2035002](https://doi.org/10.1056/NEJMoa2035002)).

Pre-print RECOVERY trial data shows for hospitalised COVID-19 patients i) a reduction of 28-days-mortality for those who were SARS-CoV-2 seronegative (anti-spike-IgG), with symptoms  $\leq 7$  days and maximum low-flow-oxygen substitution (symptoms  $\leq 7$  days: RR 0,76, low-flow oxygen substitution: RR 0,81 (0,68 – 0,97), ii) a reduced progression to mechanical ventilation (non-invasive and invasive) for those without previous mechanical ventilation: RR 0,87 (0,77 – 0,98), and iii) a reduction of hospitalisation days (median 13 vs 17 days, REGN-CoV-2 vs standard-of-care) (Horby et al. Casirivimab and imdevimabin patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial (medrxiv.org) for treatment with casirivimab and imdevimab.

Noteworthy is that 94% of patients included in the trial received additional therapy with corticosteroids. The advantages mentioned above were not evident in patients, who already received mechanical ventilation (both invasive and non-invasive). Considering the entire cohort (seropositive and seronegative patients), there was no advantage except for patients with symptoms  $\leq 7$  days (with a borderline confidence interval RR 0,87 (0,76 – 0,99)).

Contrary to data from RECOVERY trial, ACTT-3 trial showed no advantage for treatment with casirivimab and imdevimab, although no subgroup analysis considering serostatus was carried out.

Treatment with casirivimab and imdevimab is associated with a poorer clinical outcome when

administered to hospitalised COVID-19 patients requiring high-flow oxygen or mechanical ventilation. (ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD et al., A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med. 2020 Dec 22;NEJMoa2033130. doi: 10.1056/NEJMoa2033130).

The FDA has issued initial emergency use authorisation for the monoclonal antibody combination comprising casirivimab and imdevimab (21/11/2020, [www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19](http://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19)) and the combination of bamlanivimab and etesevimab ([www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0](http://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0)). A press release by the manufacturer dated 21/01/2021 pointed out that bamlanivimab exhibits a primary preventive effect among residents and staff of nursing homes. The data from this phase 3 trial (BLAZE-2) have not yet been published (<https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented>).

The current trials are monitoring the disputed risk of resistance developing during treatment with monoclonal antibodies. The extent to which the effectiveness of the monoclonal antibodies is impaired by the variants of concern (VOC) is currently the subject of ongoing investigations. Initial published results from laboratory tests indicate a significantly reduced effectiveness of bamlanivimab and etesevimab for VOC beta (B.1.351) (Wang et al, Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7, doi <https://www.nature.com/articles/s41586-021-03398-2>; 08/03/2021; Planas et al. Reduced sensitivity of infectious SARS-CoV2 variant B 1.617.2 to monoclonal antibodies and sera from convalescent and vaccinated individuals. bioRxiv 2021.05.26.445838;doi <https://doi.org/10.1101/2021.05.26.445838>). On 16/04/2021, the FDA withdrew emergency use authorisation for the United States for monotherapy with bamlanivimab due to its reduced effectiveness in the case of certain virus variants (<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab>). On 25.06.2021, the FDA also withdrew the EUA for combination therapy of bamlanivimab and etesevimab due to rising proportion of beta and gamma VOCs in the US.

Therefore, if the mutation status is unknown, combination therapy should be adjusted to the current epidemiological situation. Monotherapy with reduced effectiveness against VOC could lead to escape mutations due to incomplete virus elimination.

#### Availability and use in Germany:

The neutralizing monoclonal antibodies bamlanivimab, etesevimab and the combination of casirivimab and imdevimab are available in selected pharmacies in Germany as part of a Ministry of Health initiative. Neutralizing antibodies could be used for treatment of SARS-CoV2 infected adults and pediatric patients older than 12 years and  $\geq 40$  kg body weight.

According to the current evidence base, the use of monoclonal antibodies seems reasonable in early phase of infection, before serological conversion.

The early phase typically lasts for 7 days following symptom onset. Beyond this phase, only seronegative (anti-spike-antibody) patients with COVID-19 pneumoniae requiring maximal low-dose oxygen substitution, should be treated with monoclonal antibodies. Further clinical trials are necessary for broad applications. The authors therefore recommend to discuss each case with experienced experts from the STAKOB Infectious Diseases Advisory Network in cooperation with the DGI centres or with the nearest university clinic prior to the initiation of treatment. The contact details for the Infectious Diseases Advisory Network are available at [www.rki.de/stakob-ibn](http://www.rki.de/stakob-ibn).

Due to current epidemiological situation with increasing proportion of delta variant (B.1.617.2) the authors recommend combination therapy with two monoclonal antibodies both for immune suppressed as well as for immune competent patients in specific clinical settings. Monotherapy with bamlanivimab is not recommended, due to indications of reduced effectiveness to delta or other VOC.

	Timing	Antibody status	Preferred mAB
<b>Outpatient (asymptomatic or mild/moderate symptoms) with risk factors for severe disease progression</b>	≤ 7 days following symptom onset  Max 72 hours after positive PCR test	Within this timeframe, a negative antibody status is probable. Test results for antibody status (anti-spike) should not delay the start of therapy.	1) Casirivimab 1,2g / Imdevimab 1,2g i.v. 2) Bamlanivimab 700 mg / Etesevimab 1,4 g i.v.
<b>Hospital acquired infection, asymptomatic or mild/moderate symptoms with risk factors for severe disease progression</b>	Max 72 hours after positive PCR test	Within this timeframe, a negative antibody status is probable. Test results for antibody status (anti-spike) should not delay the start of therapy.	1) Casirivimab 1,2g / Imdevimab 1,2g i.v. 2) Bamlanivimab 700mg / Etesevimab 1,4g i.v.
<b>Hospitalized COVID 19-patients (max low-flow oxygen substitution)</b>	≤ 7 days following symptom onset	Within this timeframe, a negative antibody status is probable. Test results for antibody status (anti-spike) should not delay start of therapy.	Casirivimab 4g / Imdevimab 4g i.v.
<b>Hospitalized COVID 19-patients (max low-flow oxygen substitution)</b>	≤ 7 days following symptom onset	mAB application only with daily updated status	Casirivimab 4g / Imdevimab 4g i.v.
<b>COVID 19-patients in hospital (high-flow oxygen substitution, NIV or IMV)</b>	No indication for AB therapy		

Indications where treatment is potentially useful:

- patients infected with SARS-COV-2 in the early phase of the disease, who are (still) asymptomatic or with mild to moderate symptoms and risk factors for a severe course;
- in the context of nosocomial infections in patients with risk factors for a severe course;
- use can also be considered in the later phase of the disease among patients with high-risk factors, especially patients undergoing B cell depletion therapy and who lack the ability to

produce specific SARS-CoV-2 antibodies.

For a definition of certain high-risk groups, we refer the reader also to the STIKO Bulletin on the COVID-19 vaccination recommendation, in which the risks for COVID-19-associated mortality are presented separately (Epidemiological Bulletin 02/2021, [https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/Ausgaben/02\\_21.pdf](https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/Ausgaben/02_21.pdf)).

Moreover, administration may also be purposeful in connection with post-exposure prophylaxis, e.g. in the case of nosocomial outbreaks. There are no study findings at present, so a recommendation is currently not possible.

The possibility of allergic reactions to the aforementioned monoclonal antibodies must be taken into account, so their use should only take place under close clinical supervision.

Treatments are administered as a single intravenous infusion (infusion duration  $\geq 1$  h with follow-up  $\geq 1$  h) for both antibodies simultaneously.

### CAVE

Monoclonal antibodies should only be used in circumstances that permit the treatment of an allergic reaction (including anaphylactic shock).

Documentation:

Documentation to record side effects, outcome of treatment (e.g. hospitalised, recovered, survived) and the patient's baseline data (e.g. age, sex, risk factors) is recommended. Adverse events should be reported to the Federal Institute for Drugs and Medical Devices using the report form enclosed with the medicine. Entering the patient in a register and documenting the clinical data (including the virus variant if possible) are useful. Various databases and studies are available for this purpose (e.g. [NAPKON](#), [LEOSS.net](#), <https://studycenter.charite.de/corona/>, [WHO/ISARIC](#), [www.CAPNETZ.de](http://www.CAPNETZ.de))

Vaccination following treatment with monoclonal antibodies:

There are currently no data on the safety and effectiveness of vaccines in patients treated with a monoclonal antibody. According to data available so far, reinfection with SARS-CoV-2 seems to be very rare in the first 90 days after initial infection. Based on this low risk of reinfection and the estimated half-life of the monoclonal antibodies, a time window of 90 days after therapy with a monoclonal antibody until vaccination is recommended.

### *Convalescent plasma (CP)*

The use of convalescent plasma is another possible treatment approach. Its use on a variety of other viral infections (caused by SARS-CoV, MERS-CoV, ebola virus) yielded different results. The effectiveness of convalescent plasma is therefore the subject of critical and divergent discussion in relevant literature. Several clinical trials have been initiated. In one trial, early use (72 h after symptom onset) of a high-titre CP in mildly ill elderly patients showed reduced disease progression (Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults, [www.nejm.org/doi/full/10.1056/NEJMoa2033700](http://www.nejm.org/doi/full/10.1056/NEJMoa2033700)). A retrospective analysis from the largest US registry also revealed a correlation between clinical benefit and neutralising antibody titre (Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. January 13, 2021,

at NEJM.org. DOI: [10.1056/NEJMoa2031893](https://doi.org/10.1056/NEJMoa2031893)). Nonetheless, the evidence is not yet sufficient to permit a clear recommendation. Use as an individual attempt at treatment can be taken into consideration for critically ill patients or patients with high-risk factors, especially patients undergoing B cell depletion therapy who lack the ability to produce their own specific SARS-CoV-2 antibodies. For further information visit the web page of the CoVRIIN Expert Group at the RKI ([www.rki.de/covid-19-covriin](http://www.rki.de/covid-19-covriin))

### *Baricitinib (Olumiant®)*

Baricitinib belongs to the group of Janus kinase inhibitors and is authorised in Europe for the treatment of rheumatoid arthritis. Baricitinib exhibits anti-inflammatory and immunomodulatory effects. A variety of clinical trials have investigated and are currently investigating its administration for the treatment of COVID-19. On 19/11/2020, the FDA granted emergency use authorization for the combination of baricitinib with the antiviral drug remdesivir ('[emergency use authorization](#)' EUA). The decision is based on preliminary results from the ACTT-2 trial (NCT04401579), in which patients with a severe course were randomised for treatment with remdesivir plus baricitinib or remdesivir plus placebo. According to the manufacturer Lilly (<https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery>), the combination with baricitinib reduced the median time to recovery from 8 to 7 days, accelerated clinical recovery and reduced the proportion of patients remaining on ventilator support at day 29 (23%) compared to the group of patients receiving remdesivir alone (28%). The mortality rate up to day 29 was also slightly lower in the baricitinib plus remdesivir group compared to the remdesivir group ('Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19', DOI: [10.1056/NEJMoa2031994](https://doi.org/10.1056/NEJMoa2031994)).

The COV-Barrier trial compared treatment with baricitinib plus standard care for hospitalised patients (low-flow, high flow oxygen substitution, NIV) to those with standard care only. Although no difference was found for the combined primary end point, an effect on the secondary endpoint – 28 days mortality (RR 0,57 95% CI (0,41-0,78) was observed. The analysis of subgroups showed significant effects on patients with high-flow oxygen substitution and NIV, but not on patients without oxygen substitution or low-flow oxygen substitution. Remarkably, 80% of all patients included in the trial were treated with corticosteroids, 20% with remdesivir (Marconi VC, Ramanan AV, de Bono S, et al.: Baricitinib plus Standard of Care for Hospitalized Adults with COVID-19. medRxiv preprint: <https://doi.org/10.1101/2021.04.30.21255934> (last accessed on 10 June 2021). An analysis of a double-blinded ACTT4-trial is currently ongoing, comparing baricitinib in combination with remdesivir to dexamethasone and remdesivir.

Indication according to the FDA:

Use as part of combination therapy with remdesivir in adults and children aged 2 years and older with suspected or confirmed SARS-CoV-2 infection requiring oxygen or undergoing mechanical ventilation or extracorporeal membrane oxygenation (ECMO), dosage according to <http://pi.lilly.com/eua/baricitinib-eua-factsheet-hcp.pdf>

Use in Germany:

At present, marketing authorisation for use in Germany in connection with SARS-CoV-2 has not been issued. The authors believe that the data available so far are insufficient to justify widespread use of baricitinib alone or in combination with remdesivir; further trials are imperative. Especially the outstanding results from the ACTT4 trial are necessary to evaluate the significance of baricitinib. Where off-label use is under consideration, we strongly recommend prior discussion with colleagues in the STAKOB Infectious Diseases Advisory Network and the DGI.

### *Blockage of the interleukin-6 (IL-6) receptor*

Some patients experience the development of a situation similar to secondary virus-triggered haemophagocytic lymphohistiocytosis (sHLH, 'cytokine storm') over the course of the disease. These patients show massive inflammation, high fever and usually considerably elevated IL-6 and ferritin levels. Blockage of the interleukin-6 (IL-6) receptor is under discussion as a possible therapeutic approach in this situation. The effectiveness of blocking the IL-6 signalling pathway, e.g. with tocilizumab, sarilumab or siltuximab, is also being investigated for disease progressions that involve pneumonia and limited PaO<sub>2</sub>. Tocilizumab is authorised for the treatment of rheumatoid arthritis (RA) and Still's disease, as well as severe or life-threatening cytokine release syndrome (CRS) following CAR T cell therapy.

A placebo-controlled phase III trial on COVID-19 patients with severe pneumonia did not reveal any positive effect in terms of clinical improvement (primary endpoint) or mortality (secondary endpoint). No new safety signals were identified regarding the use of tocilizumab. (COVACTA trial of Actemra/RoActemra (Tocilizumab) in hospitalised patients with severe COVID-19 associated pneumonia, medRxiv preprint: DOI: <https://doi.org/10.1101/2020.08.27.20183442>). Preliminary findings of further trials on tocilizumab have also been published in the meantime; no improvement was shown with regard to mortality (EMPACTA, N Engl J Med 2021 Jan 7;384(1):20–30, doi: [10.1056/NEJMoa2030340](https://doi.org/10.1056/NEJMoa2030340), BACC Bay N Engl J Med . 2020 Dec 10; 383(24):2333–2344, doi: [10.1056/NEJMoa2028836](https://doi.org/10.1056/NEJMoa2028836)). An initial publication on another interleukin-6 receptor blocker (sarilumab) revealed similar results (<https://www.sanofi.com/en/media-room/press-releases/2020/2020-09-01-07-00-00>). More recent data have shown improved outcomes in critically ill patients when IL-6 receptor antagonists (tocilizumab and sarilumab) are used in combination with corticosteroids (Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 - The REMAP-CAP Investigators, <https://www.nejm.org/doi/full/10.1056/NEJMoa2100433>). Recently published findings of the RECOVERY Trial (RECOVERY Collaborative Group, Horby PW, Pessoa-Amorim G et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*: 2021; 397:1637-45) showed evidence of reduced mortality in hospitalised patients with oxygen requirements and clinical inflammation, especially during the early phase of the disease ( $\leq 7$  days) or if corticosteroids are also administered. This effect tended to be most pronounced among patients that at the time did not require invasive mechanical ventilation. The use of tocilizumab reduced the risk of invasive ventilation in this patient group (RR 0.81 (95% CI 0.68–0.95)). Administering tocilizumab to patients already receiving mechanical ventilation had no effect on ventilation duration.

#### Use in Germany

There is currently no authorisation usage as SARS-CoV2 treatment in Germany. Due to previous findings, the AWMF S3-guideline recommend tocilizumab for patients with severe disease progression, but not for patients without need for oxygen substitution or only low-flow oxygen substitution and for patients that are mechanically ventilated (113-001LGI\_S3\_Empfehlungen-zur-stationaeren-Therapie-von-Patienten-mit-COVID-19\_\_2021-05.pdf (awmf.org)). The authors believe tocilizumab should be used in case of CRP  $\geq 75$  mg/l, bilateral ground-glass opacities and increasing need for oxygen substitution despite dexamethasone therapy. The authors do not recommend tocilizumab for later disease stages.

### *Ivermectin (Scabiora®)*

The anti-parasitic drug ivermectin has been and continues to be investigated in a wide variety of

clinical trials on COVID-19. Nonetheless, the authors do not believe that the current data do not provide adequate proof of its effectiveness. Administration of ivermectin should therefore take place only within the framework of clinical trials.

### *Colchicine*

A meta-analysis published as a preprint compared three randomised controlled trials in which colchicine was investigated on a total of 4665 patients (Chiu L et al, [www.medrxiv.org/content/10.1101/2021.02.02.21250960v2](https://www.medrxiv.org/content/10.1101/2021.02.02.21250960v2)). By far the largest trial included high-risk patients with mild COVID-19 symptoms, while the two smaller trials involved hospitalised patients with COVID-19 disease of varying severity who did not require ventilation. One of them was conducted as an open-label trial, while the other two were blinded, Only the largest of these trials is currently available in the form of a preprint. The difference to placebo in terms of mortality is not statistically significant (odds ratio 0.49 [95% CI: 0.20, 1.24]). In addition, two of the trials investigated the risk of intensive ventilation requirements or normal ventilation requirements. The individual trials did not reveal any statistically significant effects in this regard. Colchicine is also under investigation as part of the British ReCoVeRy trial. According to press reports, more than 6500 patients have already been randomised to this arm, but results are not yet available.

The data available at this point are not sufficient to confirm effectiveness. It follows, therefore, that colchicine should exclusively be administered within the framework of clinical trials.

### *Budesonide*

The STOIC Trial1, published on 09/04/2021, and the interim evaluation of the PRINCIPLE Trial2, which was published as a preprint on 12/04/2021, investigated the effectiveness of budesonide, an inhaled steroid, with regard to clinical endpoints such as rate of emergency medical consultations (including hospitalisation), symptom duration and intensity, oxygen saturation and viral load.

In the authors' opinion, the data presented here are not yet sufficient for a recommendation due to various limitations of the studies and therefore currently see no indication for an off-label use of budesonide or other inhaled steroids, neither in outpatients nor in currently hospitalised patients. For a detailed assessment of the use of budesonide in COVID 19, we refer to the recently published statement by the German Respiratory Society (DGP), the Austrian Society for Pneumology (ÖGP) and the German Society for Allergology and Clinical Immunology (DGAKI) ([https://pneumologie.de/fileadmin/user\\_upload/COVID-19/20210419\\_DGP\\_OEGP\\_DGAKI\\_C19\\_und\\_ICSt\\_STOIC-Studie.pdf](https://pneumologie.de/fileadmin/user_upload/COVID-19/20210419_DGP_OEGP_DGAKI_C19_und_ICSt_STOIC-Studie.pdf)), as well as to the joint [statement by the COVRIIN Expert Group, STAKOB and DGI](#).

### *Other substances under investigation:*

There are currently several hundred substances in various stages of research. Comments on a small selection of substances are available on the web page of the COVRIIN Expert Group at the RKI ([www.rki.de/covid-19-covriin](http://www.rki.de/covid-19-covriin)). This document is updated regularly.

### ***Treatment with antibiotics:***

In patients with a suspected bacterial superinfection and/or septic course, calculated antibiotic treatment should be initiated immediately in accordance with the guidelines and within one hour in the case of septic shock. Antibiotic treatment should be discontinued within 48 h if there is no evidence of pathogens and procalcitonin is normal. Prophylactic administration of antibiotics is not recommended without indication of a bacterial infection.

## Pre- and post-exposure prophylaxis

There are currently no data on the effectiveness of medicinal pre- or post-exposure prophylaxis. At present, it is recommended neither for contact persons nor for medical personnel. Various clinical trials are ongoing and their findings are pending.

## De-isolation and discharge management

Notes on de-isolation and discharge management are available on the RKI website at [www.rki.de/covid-19-entlassungskriterien](http://www.rki.de/covid-19-entlassungskriterien).

## Aftercare and follow-up

Routine clinical follow-up after discharge from inpatient care is not recommended as a regular procedure, but should take place depending on the clinical course. Patients should certainly consult a doctor in the event that their symptoms intensify.

Instructions for patients after discharge:

An elevated risk of contracting other infections may exist temporarily, so clinical self-monitoring is recommended for 14 days. General hygiene measures should also continue to be observed.

## Notes for pregnant mothers and children

Current evidence does not suggest that pregnant women infected with SARS-CoV-2 are exposed to a significant risk of a severe course compared to non-pregnant women of the same health status (Chen et al. Lancet 2020). No intrauterine or perinatal transmission occurs in the vast majority of cases (Yang and Liu, Am J Perinatol, 2020). Participating professional associations have compiled infectious disease recommendations for dealing with COVID-19 during pregnancy, around the time of birth and in the puerperium (<https://dgpi.de/aktualisierte-stellungnahme-von-dgpm-dggg-dgpgm-dgpi-und-gnpi-zu-sars-cov-2-covid-19-und-schwangerschaft-geburt-und-wochenbett-stand-30-06-2020/>, as of 02/10/2020, last retrieved on 28/04/2021).

SARS-CoV-2 infection in paediatric patients predominantly manifests itself as an uncomplicated disease of the upper and lower airways. However, serious complications or fatalities may occur among children in rare cases (Hoang et al, CoVID in 7780 pediatric patients, a systematic Review, EClinical Medicine 2020, 1000433)

Reports of children with severe multisystem inflammatory syndrome associated with the current pandemic have become more frequent since the end of April 2020 (Pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS) or synonymously multisystem inflammatory syndrome in children (MIS-C). According to CDC classification, MIS-C applies if the following criteria are satisfied:

- 'An individual aged <21 years presenting with fever, laboratory evidence of inflammation'

**AND**

- 'Evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematological, gastrointestinal, dermatologic or neurological)'

**AND**

- 'No alternative plausible diagnoses'

**AND**

- 'Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.'

This severe acute disease may be fatal in rare cases if it is not detected early on and treated with anti-inflammatory and intensive medical care (Kaushik et al., PIDJ, 2020, Dufort et al., NEJM, 2020, Feldstein et al., NEJM, 2020). A recently released systematic review of over 650 published MIS-C cases to date indicated that 71% of patients required intensive care. A predominant share experienced gastrointestinal symptoms with cardiac involvement. The principal form of treatment was intravenous immunoglobulins and systemic steroids (Ahmed et al, Eclinical Medicine 00(2020)100527).

In regard to other recommended treatments for children with COVID-19, we refer the reader to the current statement by the German Society for Pediatric Infectious Diseases (<https://dqpi.de/stellungnahme-medikamentoesen-behandlung-kindern-covid-19/>).

## Bibliography and further literature

1. WHO: **Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)**. 2020.
2. Cai Jiehao<sup>1†</sup> XJ, Lin Daojiong<sup>3†</sup>, Yang zhi<sup>4</sup>, Xu Lei<sup>5</sup>, Qu Zhenghai<sup>5</sup>, Zhang Yuehua<sup>6</sup>, Zhang Hua<sup>7</sup>, Jia Ran<sup>2</sup>, Liu pengcheng<sup>2</sup>, Wang Xiangshi<sup>1</sup>, Ge Yanling<sup>1</sup>, Xia Aimei<sup>1</sup>, Tian He<sup>1</sup>, Chang Hailing<sup>1</sup>, Wang Chuning<sup>1</sup>, Li Jingjing<sup>1</sup>, Wang Jianshe<sup>1</sup>, Zeng Mei<sup>1</sup>: **A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features**. 2020.
3. Chaolin Huang\* YW, Xingwang Li\*, Lili Ren\*, Jianping Zhao\*, Yi Hu\*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu,, Zhenshun Cheng TY, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie,, Guangfa Wang RJ, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†: **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China**. 2020.
4. Qifang Bi 1, Yongsheng Wu 2,#, Shujiang Mei 2,#, Chenfei Ye 3,4,#, Xuan Zou 2, Zhen Zhang 2,, Xiaojian Liu 2 LW, Shaun A. Truelove 1, Tong Zhang 4, Wei Gao 2, Cong Cheng 2, Xiujuan, Tang 2 XW, Yu Wu 2, Binbin Sun 3,4, Suli Huang 2, Yu Sun 4, Juncen Zhang 4, Ting Ma, 3, \*, Justin Lessler 1, \*, Tiejian Feng 2, \*: **Epidemiology and Transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts**. 2020.
5. RKI: **SARS-CoV-2 Steckbrief zur Coronavirus-Krankheit-2019 (COVID-19)**.
6. Wei-jie Guan 1\* PD, Zheng-yi Ni 2\*, M.D., Yu Hu 3\*, M.D., Wen-hua Liang 1,4\*, Ph. D., Chun-quan Ou 5\*, MSc., Jian-xing He 1,6\*, M.D., Lei Liu 7,8\*, M.D., Hong Shan 9\*, M.D., Chun-liang Lei 10\*, M.D., David S.C. Hui 11\*, M.D., Bin Du 12\*, M.D., Lan-juan Li 13\*, M.D., Guang Zeng 14\*, MSc., Kwok-Yung Yuen 15\*, Ph.D., on behalf of China Medical Treatment Expert Group for 2019-nCoV: **Clinical characteristics of 2019 novel coronavirus infection in China** 2020.
7. Fei Zhou\*, Ting Yu\*, Ronghui Du\*, Guohui Fan\*, Ying Liu\*, Zhibo Liu\*, Jie Xiang\*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao: **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort trial** 2020
8. Waleed Alhazzani, Morten Hylander Møller, [...]Andrew Rhodes: **Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19)** Intensive Care Medicine (2020)
9. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, et al: **Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China**. JAMA Intern Med 2020)
10. Beigel John H. et al: **Remdesivir for the Treatment of Covid-19— Preliminary Report**. doi: 10.1056/NEJMoa2007764.
11. Li H, Chen C, Hu F, Wang J, Zhao Q, Gale RP, Liang Y: **Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis**. *Leukemia* 2020
12. Peter Horby, Martin J Landray et al, RECOVERY Collaborative Group: **Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report**, NEJM 17/07/2020 DOI: 10.1056/NEJMoa2021436
13. WHO - Corticosteroids for COVID-19 Living Guidance, <https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1>
14. WHO - Therapeutics and COVID-19: living guideline, <https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline>

### Note

*As an independent body, STAKOB publishes statements on clinical issues relating to diseases caused by highly pathogenic and life-threatening pathogens on its own responsibility. The opinions are based on the current state of scientific knowledge, information from prestigious health institutions and empirical values obtained by STAKOB. Their applicability must be reviewed on a case-by-case basis.*