COVID-19

A practical guideline for healthcare professionals in Afghanistan

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This guideline and future updates will be available at: www.mcan.nu

Contents

Foreword

This document is intended for clinicians involved in the care of patients with Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection in Afghanistan. This document is not meant to replace clinical judgment or specialist consultation but rather to strengthen clinical management of these patients and to provide up-to-date guidance, taking the limited healthcare resources in Afghanistan into consideration.

This guideline is the result of cooperation between Medical Committee Afghanistan-Netherlands (MCAN) and Dutch-Afghan clinicians (see list of guideline development members) who are directly and indirectly involved in the care of COVID-19 patients.

MCAN and the guideline development members will continue to monitor the situation closely and will issue an update if necessary. Clinicians who have questions and/or comments are welcome and encouraged to provide their feedback on this guideline by contacting MCAN by mail (info@mcan.nu) or FB (Medical Committee Afghanistan-Netherlands). This guideline and further updates will be available at www.mcan.nu.

Guideline development members

Fagirzada (Ashraf), MD
General Practitioner, GC t Slag, Rotterdam, The Netherlands
Fanyar (Zabihullah), MD
Pulmonologist, Zorgzaam hospital, Terneuzen, The Netherlands
Ghariq (Ismael), MD
Anesthesiologist, Leiden University Medical Centre, The Netherlands
Hashemi (Sayed MS), MD
Pulmonologist, Amsterdam University Medical Centers (VU), The Netherlands
Karim (Faiz), MD, PhD
Internist, Groene Hart Hospital, Gouda, The Netherlands
Nadery-Siddiqi (Laima), MD, PhD
Internist-nephrologist, Haaglanden Medical Center, The Hague, The Netherlands
Nur (Erfan), MD, PhD
Internist-hematologist, Amsterdam University Medical Centers, The Netherlands
Oriakheil (Hogaei), MD
Resident Pulmonology, University Medical Center Utrecht, The Netherlands
Rahim (Niloufar), MD
Resident General Practitioner, Radboud University, Nijmegen, The Netherlands
Roshanmal (Zubeer), MD
Resident GP, resident in pediatrics (NICU), UMCU, Utrecht, The Netherlands
Salah (Khibar), MD, PhD
Resident Radiology, RadboudUMC, Nijmegen, The Netherlands
Samim (Morsal), MD, PhD
Resident Radiology, University Medical Center Utrecht, The Netherlands
Zewari (Said Safir), MD, PhD candidate
Resident Pulmonology, St. Antonius hospital, Nieuwegein, The Netherlands

1. Background

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in a pandemic throughout the world. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is just as SARS a beta-coronavirus which also uses the ACE2 receptor for cell entry. Two different types of SARS-CoV-2 are identified, designated type L (accounting for 70 percent of the strains) and type S (accounting for 30 percent). Main transmission route is via respiratory droplets through direct contact with the mucous membranes. Infection can also occur by touching your eyes, nose or mouth with the acquired contagion from polluted surfaces. Studies have shown that patients with symptoms have higher viral load from the upper respiratory specimen than before which suggest that symptomatic patients are more contagious, however transmission of the disease by asymptomatic patients has been described. Furthermore, transmission can occur during 48 hours before becoming symptomatic. Viral shedding has been reported for 21 days of the disease nevertheless patients later in the illness are less contagious than the first 7 days of the symptoms. The incubation period for COVID-19 is thought to be within 14 days following exposure, with most cases occurring approximately four to five days after exposure.

2. Diagnosing COVID-19

2.1 Symptoms and clinical examination

Majority of the patients are asymptomatic or have mild symptoms (81%). Almost 14% of COVID-19 patients develop severe disease (hypoxia and/or > 50% lung involvement). Around 5% develop critical disease with shock and multi-organ failure. Overall case fatality is estimated around 2 - 3%. Majority of patients have flu like symptoms (fever, dry cough, sore throat, rhinorrhea, fatigue and muscle ache). A portion of patients exhibit breathing difficulties (dyspnea) and other symptoms (chest pain, sputum production, hemoptysis) seen in common pneumonia. Symptoms like loss of smell and taste and conjunctivitis have also been described. Development of acute respiratory distress syndrome (ARDS), hyperinflammation syndrome (HIS) and multi-organ involvement may result in progressive respiratory failure and even death. Around 5% of the patients exhibit gastro-intestinal symptoms (diarrhea, nausea, vomiting and abdominal pain).

2.2 Main Laboratory and additional tests

The following laboratory evaluations are recommended in patients with confirmed or suspected COVI-19 who are to be admitted. While some of these results will help determine the severity of the disease in these patients, other have prognostic value. Together with the clinical findings, these laboratory results will help the treating physician in making treatment decisions. This is a practical guideline for performing laboratory tests. Some of the listed tests might not be available locally.

Patients to be admitted with suspected or confirmed COVID-19 should have the following tests performed:

- Complete blood count (CBC) with differential (leucocyte diff).
- For patients with confirmed COVID-19, consider baseline D-dimer quantification (associated with the risk of venous thrombo-embolism and cardio-vascular injury), ferritin level (predictor of COVID-19 associated HIS), CRP (disease severity and predictor of bacterial superinfection), PT/INR, PTT, fibrinogen (diffuse intravascular coagulation = DIC), LDH, and procalcitonin (predictor of bacterial superinfection) testing for prognostic indications.
- Glucose, creatinine, albumin, potassium, sodium, alkaline phosphatase, alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin.
- SARS-CoV-2 RNA detection test, e.g. RT-PCR on nasopharyngeal swab if previously not performed. In case of a negative PCR for SARS-CoV-2 but a strong clinical suspicion, if possible, perform a complete respiratory pathogen panel (RPP) to find an alternative explanation (such as influenza A and B, RSV, parainfluenza 1,2,3,4, human metapneumovirus, rhinovirus/enterovirus, adenovirus). In febrile patients, obtain routine work-up for infection, including blood cultures.
- Chest X-ray (or chest ultrasound or for some indications Chest CT). See Radiology evaluations.
- Note that elevated D-dimer alone is not sufficient for predicting venous thrombo-embolism. Clinical alertness is necessary. See Treatment considerations for the use of anticoagulants as thrombosis prophylaxis due to the increased risk of potentially life threating pulmonary embolism and cardiovascular injury during COVID-19.
- Serial monitoring of inflammatory markers is not recommended. Need for repeat testing of inflammatory markers may be discussed at daily evaluation of COVID-19 patients.
- Troponin and BNP should not be routinely measured in the absence of other evidence of myocardial injury or congestive heart failure.
- ECG to monitor signs of cardiac injury and potential predictors of arrhythmias (especially QT time).

For patients with confirmed COVID-19 and an elevated baseline D-dimer or other signs of DIC (low fibrinogen, abnormal PT/INR or PTT not on anticoagulation), consider daily CBC with diff, D-dimer, PT/INR, PTT, fibrinogen, CRP and creatinine.

For patients with confirmed COVID-19 and normal baseline D-dimer, consider CBC with diff and repeating D-dimer quant, PT/INR, PTT, fibrinogen, CRP and creatinine every other day or upon clinical deterioration.

2.3 PCR and collection of specimens for laboratory diagnosis

COVID-19 is diagnosed with direct detection of SARS-CoV-2 RNA by real-time polymerase chain reaction (RT-PCR) of nasopharyngeal samples. If the patient can produce sputum, it can also be sent for PCR as it might have a better yield. Lower respiratory tract samples with bronchoscopy should generally be avoided due to the risk of aeroslization of virus during this procedure.

Sampling
Sampling should be performed by an experienced person to avoid false-negative results. Sample as deep as possible! (for the throat swab: until the patient starts gagging). Please read the user manual of the specific swabs used at your center. In general for the SARS-CoV-2 diagnostics, two separate smears of the nasopharynx and throat are preferably tested in combination, after which one result will follow. If the thin flexible nasopharyngeal swab is not available for the smear of the nasal cavity, a throat swab may be sufficient. If the patient can produce sputum, it can be used as an alternative, especially in patients with negative first PCR but high clinical suspicion and no alternative explanation.
Collect the samples in the tube with the special medium for virology and seal the tube as specified in the manual. Disinfect the sealed tube with non-alcoholic disinfectants. Do not disinfect with alcohol, as it makes the labels on the tube illegible.
Transportation of the swabs to the lab should be according to manufacturer's guidelines.

Repeat COVID-19 Testing in Symptomatic Patients
Repeat SARS-CoV-2 testing should be considered in case of a continued high index of suspicion in the presence of a negative COVID-19 test result, a negative respiratory pathogen panel (RPP), and a lack of alternative diagnosis. Examples include the following:

- Patient has developed additional or worsening symptoms since the time of initial testing, such as development of a new fever in a patient with a persistent cough.
- Patient has persistent symptoms, such as cough, AND consistent chest imaging or lab results (e.g. lymphopenia).
- Checking additional COVID-19 tests from a nasopharyngeal source for a patient who has already had two negative tests is not recommended, unless the patient clearly develops new symptoms which may indicate a *newly acquired* COVID-19 infection.

Repeat COVID-19 testing of outpatients should be avoided unless patients develop new symptoms concerning for newly acquired infection or worsening symptoms which may indicate need for admission.

2.4 The role of Chest Imaging in the management of patients during COVID-19

Chest-X-ray
Chest-X-ray (CXR) is insensitive in mild or early COVID-19 infection (Figure 1). However, if patients present at a later stage of the disease with more severe respiratory symptoms, CXR may be abnormal and be of diagnostic value. Equipment portability within an infected patient's isolation room is another factor that may favor CXR in selected populations, effectively eliminating the risk of COVID-19 transmission along the transport route to a CT scanner and within the room housing a CT scanner, particularly in environments lacking PPE. In hospitalized patients CXR can be useful for assessing disease progression and alternative diagnoses such as lobar pneumonia suggestive of bacterial superinfection, pneumothorax and pleural effusion.

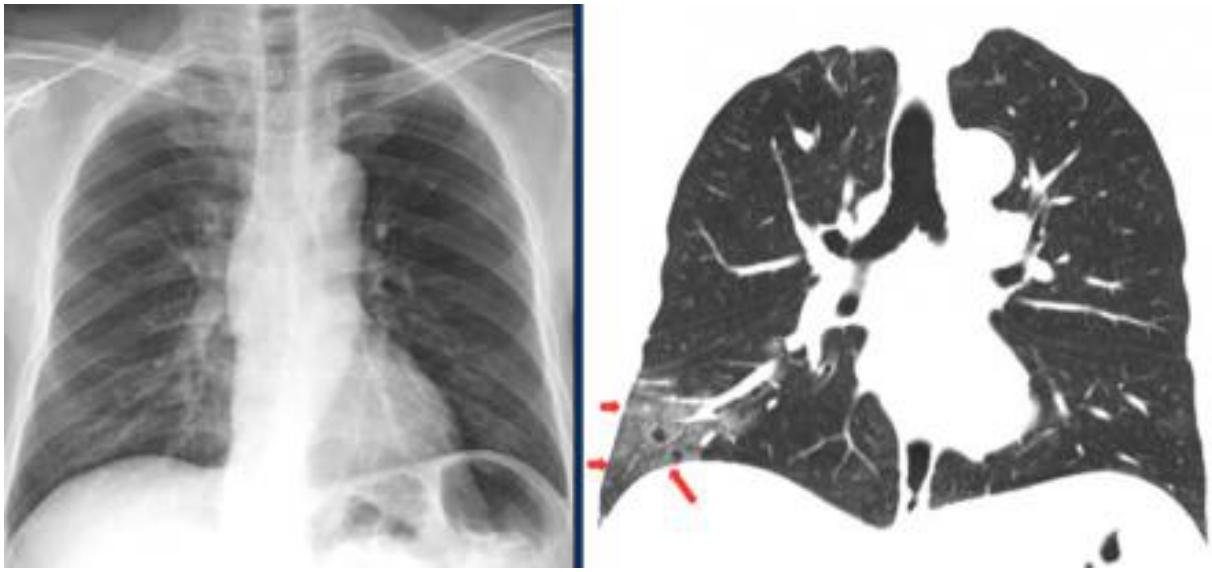


Figure 1. Comparison of CXR and coronal CT images of same patient demonstrates ground-glass opacification in the right lower lobe on CT which is not visible on the CXR performed within 1 hour.

The primary findings of covid-19 pneumonia on CXR are those of atypical pneumonia or organizing pneumonia. Of patients with COVID-19 requiring hospitalization, 69% had an abnormal chest radiograph upon admission, while 80% had radiographic abnormalities sometime during hospitalization. Important findings suggesting covid-19 pneumonia on CXR are bilateral or multilobar ground-glass opacification or consolidations (Figure 2). Peripheral and lower zone distribution of the airspace opacifications favors covid-19 pneumonia (or another atypical pneumonia). The airspace opacifications on CXR can be obvious (Figure 3) but often are very subtle (Figure 4). Pleural effusion is rare. In some cases, CXR can also help differentiate between other causes of dyspnea. For example, look for signs of cardiac decompensation or lobar pneumonia.

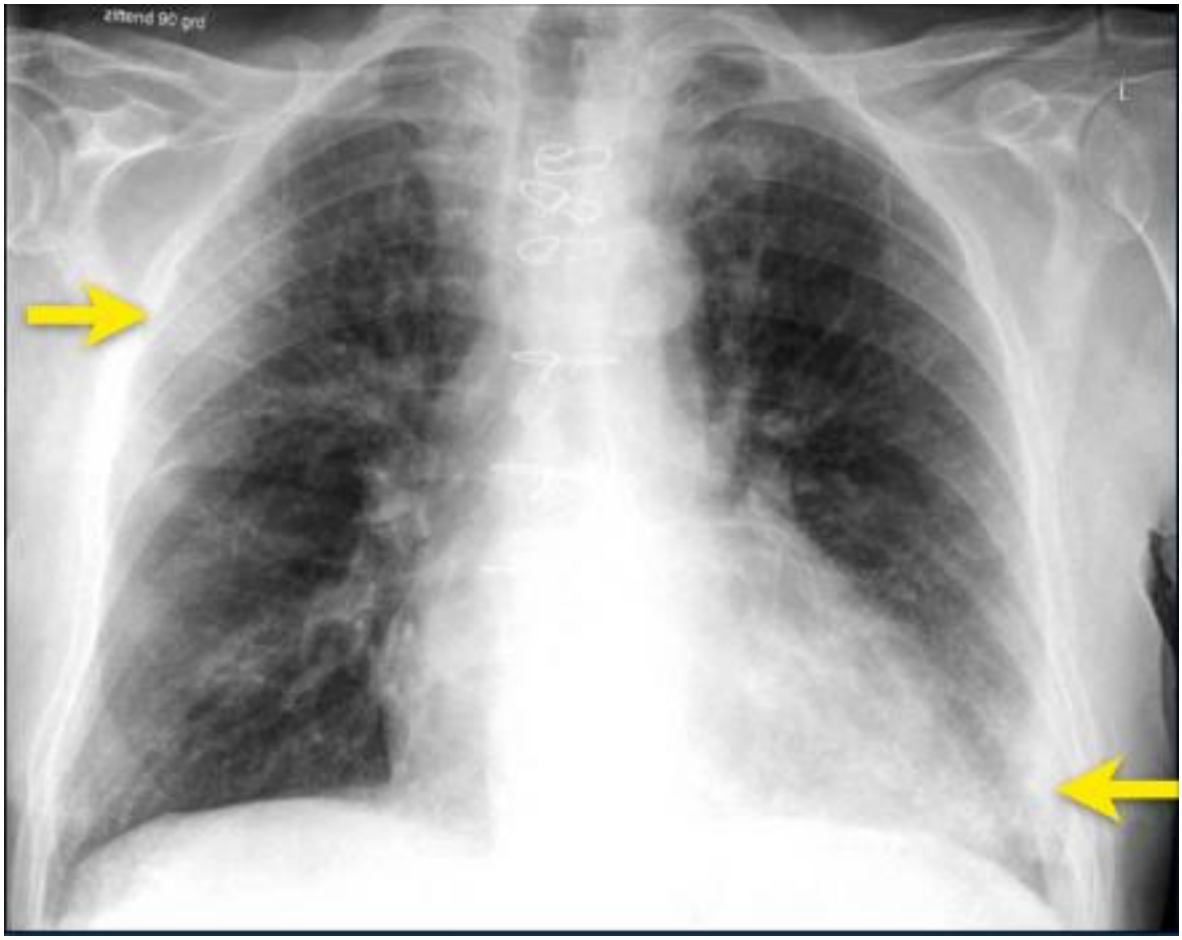


Figure 2. CXR of 83-year-old male with covid-19 infection shows ground-glass opacification and consolidation in the upper lobe and left lower lobe (arrows).

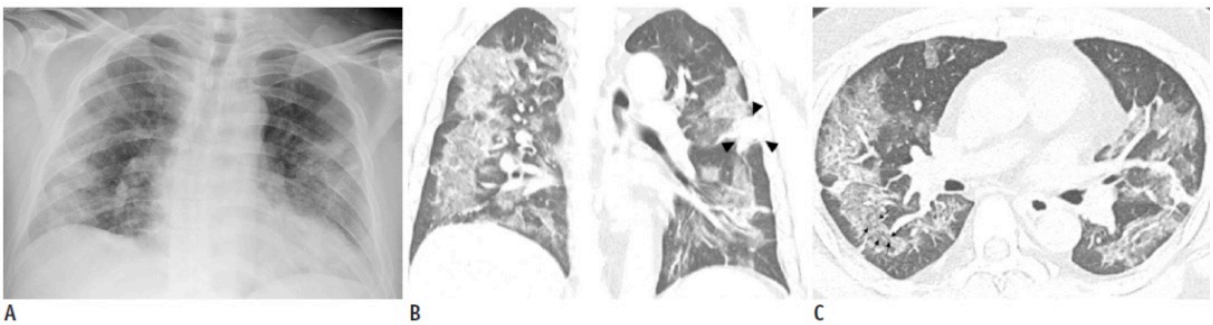


Figure 3. Representative CXR (A) and CT images (B, C) of COVID-19 pneumonia manifesting as confluent mixed ground-glass opacities and consolidation on CT. A. Anteroposterior chest radiograph shows multifocal patchy peripheral consolidations in bilateral lungs, except for left upper lung zone. B, C. Coronal and axial chest CT images show confluent mixed ground-glass opacities and consolidative lesions in peripheral bilateral lungs.

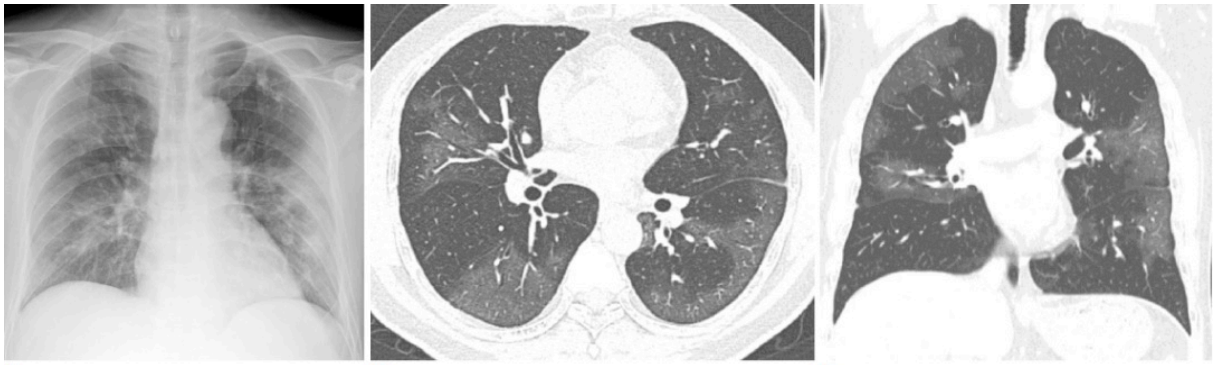


Figure 4. Representative chest radiographic (A) and CT images (B, C) of COVID-19 pneumonia manifesting as confluent pure ground-glass opacities on CT. A. Baseline anteroposterior chest radiograph shows patchy ground-glass opacities in right upper and lower lung zones and patchy consolidation in left middle to lower lung zones. B, C. Baseline axial and coronal chest CT images show confluent pure ground-glass opacities involving both lungs.

Ultrasound

Lung ultrasound may be useful in the evaluation of critically ill COVID-19 patients. The following patterns have been observed, tending to have a bilateral and posterobasal predominance. Multiple B-lines, which are comet-tail artifacts arising from the pleural line. Furthermore, irregular, thickened pleural line, subpleural consolidations and alveolar consolidation are described on ultrasounds. Another way that ultrasound may be of value would be in patient with suspected pulmonary embolism (for example in patients with hemodynamic instability and presence of severe right ventricular dysfunction). Echocardiographic features which may be suggestive include thrombus-in-transit, right ventricular dysfunction commonly dilated and hypocontractile, flattening or dyskinesis of the interventricular septum.

Indications for Chest CT

According to current diagnostic criteria, viral nucleic acid detection using real-time polymerase chain reaction (RT-PCR) remains the standard of reference with very high specificity. However, false negative RT-PCR tests have been reported in patients with computed tomography (CT) findings of COVID-19 who were eventually tested positive with serial sampling. Furthermore, previous studies have shown high sensitivity of chest CT for diagnosing COVID-19. Another problem with the RT-PCR test is that the test results can take up to 24 hours while CT results are immediately available. The greater sensitivity of CT combined with the non-invasive character of the modality with high accuracy and speed, may support the use of chest CT for evaluating of patients with clinical features compatible with COVID-19 in the setting of a public health approach that requires isolation of all infected patients within an environment where the reliability of COVID-19 testing is limited. However, it should be noted that chest CT may be negative for viral pneumonia of COVID-19 at initial presentation (0-2 days after symptoms onset).

CT is more sensitive for early parenchymal lung disease compared with Chest X-ray, disease progression, and alternative diagnoses including acute heart failure from COVID-19 myocardial injury and when acquired with intravenous contrast material, pulmonary thromboembolism (PE). In patients with suspected COVID-19 as well as a high clinical

suspicion for PE (e.g. based on hemoptysis, unexplained tachycardia, or signs/symptoms of DVT, acute deterioration upon moving patient), CT pulmonary angiography should be considered if the D-dimer level is elevated. The D-dimer threshold used should follow locally used algorithms, i.e. ≥500 mg/L, age-adjusted threshold, or ≥1,000 mg/L when no YEARS criteria are present. If PE is confirmed, therapeutic anticoagulation is indicated. Leveraging these superior capabilities depends upon the availability of CT capacity.

The most recent Fleischner Society consensus statement has proposed that chest imaging is not indicated as a screening tool in asymptomatic or mild clinical feature patients, while chest CT is indicated in patients with moderate to severe features of COVID-19, regardless of the laboratory test results and in patient with COVID-19 and worsening respiratory status where imaging will impact management. Regardless of the local recommendation and availability radiologists should familiarize themselves with the CT appearance of COVID-19 infection in order to be able to identify findings consistent with infection in patients imaged for other reasons.

Chest CT protocol
Preferably non-contrast chest CT, reconstructions of the volume at 0.625 mm to 1.5 mm slice thickness (gapless). CT should be performed during inspiration. If administration of iodinated contrast medium is indicated, for example for detection of pulmonary embolism, beware that the contrast may impact the interpretation of ground-glass opacification patterns.

CT-findings
Initial CT-findings in COVID-19 cases include ground-glass opacification (GGO) with or without consolidations, in lung regions close to visceral pleural surfaces, including the fissures, and a multifocal bilateral distribution. These GGO's often show (half) rounded and un-sharp demarcation, but can be accompanied by sharply delineated ground-glass areas that outline the shape of multiple adjacent secondary pulmonary lobules. Sometimes there are thickened interlobular and intralobular lines in combination with a ground glass pattern. This is called crazy paving. As the disease progresses, increasing consolidations occur within the ground-glass areas. In the early phase of the disease the GGO's may present as a unifocal lesion, most commonly located in the inferior lobe of the right lung. Finally, opacities occur that resemble organizing pneumonia, such as reverse halo signs or ground glass with extensive subpleural consolidations and air bronchograms. Subpleural curvilinear bands or bands of ground glass with or without consolidation in a tethered, arching pattern with small connections to the pleura are also considered typical. Thickened vessels within lung abnormalities are typical and frequently found in all other confirmatory patterns. Consolidation superimposed on GGO's as the initial imaging presentation is found in a smaller number of cases, mainly in the elderly population. Septal thickening, bronchiectasis, pleural thickening, and subpleural involvement are some of the less common findings, mainly in the later stages of the disease. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, reversed halo sign, and pneumothorax are some of the uncommon but possible findings seen with disease progression. There is much overlap of the CT-pattern of COVID-19 with other viral pneumonias. Figure 5 and 6 shows the typical findings of COVID-19 and mention the findings that are very atypical, that are arguments against the diagnosis of COVID-19 and figure 7 shows the changes over time.

intitial CT-patterns in COVID-19

Ground-glass opacification	88%
Bilateral involvement	88%
Posterior distribution	80%
Multilobar involvement	79%
Peripheral distribution	76%
Consolidation	32%

Typical findings	Atypical findings
Multifocal groundglass opacities	Central or peribronchovascular
Peripheral and basal distribution	More apical distribution
Unsharp demarcation	Lymphadenopathy *
Vascular thickening	
Round	**Very Atypical**
Crazy paving	Cavitation - calcification
Ground glass and Consolidations	Tree-in-bud, bronchiolitis
(Reversed) halo	Nodular pattern
Spider web	Mass
	Pleural thickening

Figure 5. Common Patterns and Distribution on Initial CT Images of 919 patients COVID-19 and typical vs atypical findings in COVID-19.

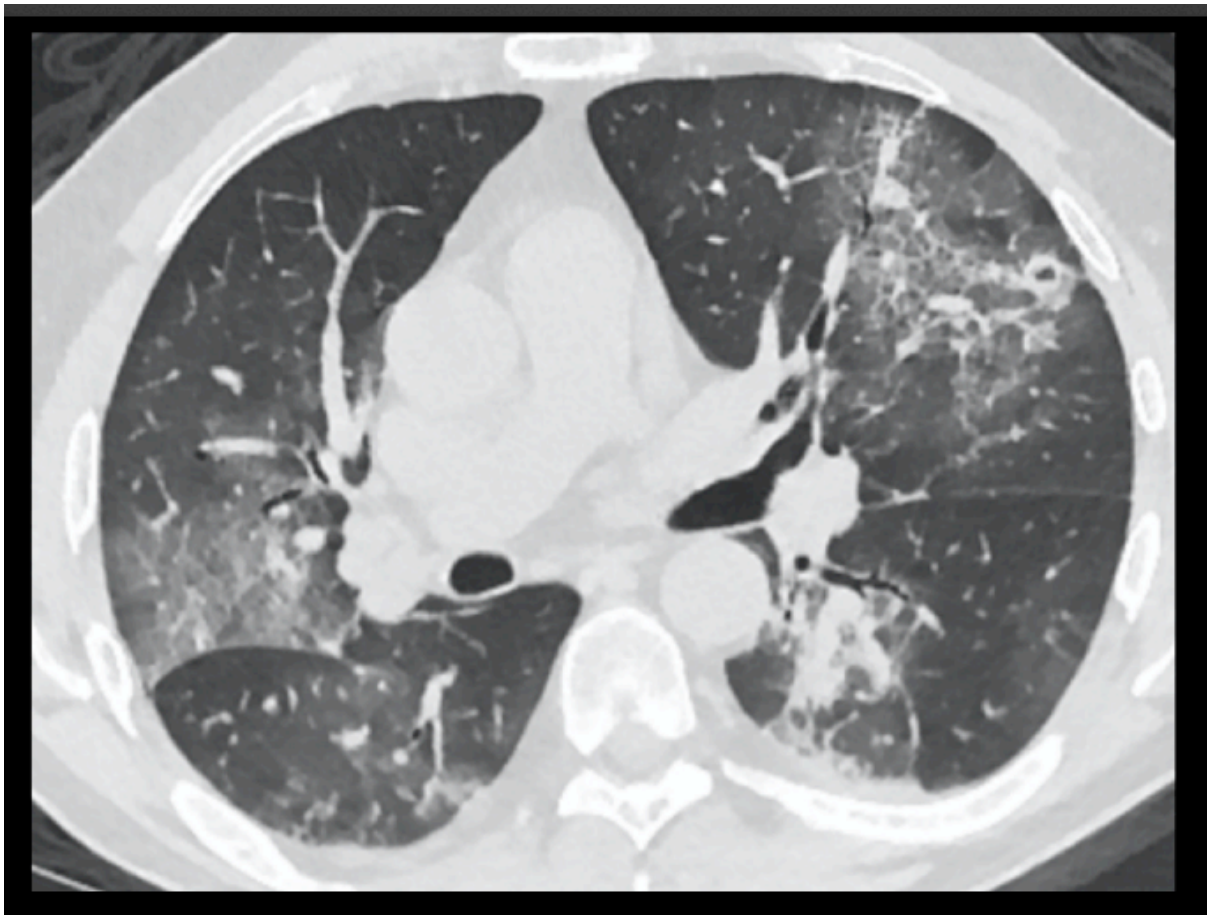


Figure 6. Typical COVID-19 chest CT with multifocal bilateral subpleural ground-glass opacities on the right in contact with the major fissure, crazy paving on the left upper lobe and consolidation on the left lower lobe.

CT-changes over time		
Early stage	0-4 days	GGO, partial crazy paving, lower number of involved lobes
Progressive stage	5-8 days	Progressive (5-8 days): Extension of GGO, increased crazy paving pattern
Peak stage	10-13 days	Consolidation
Absorption stage	≥14 days	Gradual resolution

Figure 7. Changes over time.

The CT-findings of COVID-19 show overlap with other diseases like:

- H1N1 influenza
- Other viral pneumonia; adenovirus, CMV
- Organizing pneumonia
- Acute interstitial pneumonitis

The Dutch Radiological Society has developed the COVID-19 Reporting and Data System (CO-RADS), which can be used in the clinic and provides a reporting scheme for COVID-19 in which the level of suspicion of COVID-19 infection is graded from very low or CO-RADS 1 up to very high or CO-RADS 5 (Appendix A).

Conclusions

According to the available data CRX is insensitive in mild or early COVID-19 infection and may be abnormal in patients with advanced symptoms. In hospitalized patients CXR can be useful for assessing disease progression and alternative diagnoses. Lung ultrasound may be useful in the evaluation of critically ill COVID-19 patients and in patient with suspected pulmonary embolism and in the presence of hemodynamic compromise to assess the presence of severe right ventricular dysfunction. Chest-CT imaging is more sensitive for early parenchymal lung disease, disease progression, and alternative diagnoses including acute heart failure from COVID-19 myocardial injury. According to the consensus statement of the Fleischner Society CT-imaging is indicated in patients with moderate to severe features of COVID-19, regardless of the laboratory test results. The typical CT-findings in COVID-19 cases include GGO's with or without consolidations, in lung regions close to visceral pleural surfaces, including the fissures, and a multifocal bilateral distribution.

3. Screening and triage: early recognition of patients with COVID-19 outside the hospital

Disease course

The symptoms of COVID-19 usually start gradually and are often mild in nature. The majority, 80% of patients, recover without specific treatment. The exact duration of the complaints is very variable and also depends on whether complications arise. Older patients (> 60 years) and the chronically ill have an increased risk of a fatal course.

Risk factors for a severe course of disease
Patients with an increased risk of a serious course are:

- elderly ≥ 60 years
- patients> 18 years * with:
    - Chronic abnormalities and functional disorders of the airways and lungs;
    - Chronic heart disease;
    - Diabetes mellitus;
    - Severe kidney disease leading to dialysis or kidney transplantation; reduced resistance to infections: medication for autoimmune diseases, after organ transplantation, for hematological disorders, for (functional asplenia), for congenital or later-developed immune disorders that require treatment, or for cancer if the patient is receiving chemotherapy and/or radiation;
    - An untreated HIV infection or an HIV infection with a CD4 number <200 / mm3.
    - Obesity

* Children up to the age of 18 with underlying suffering are currently not covered by these additional recommendations. Based on age-specific incidence data, the risk of COVID-19 is significantly lower in children. In addition, virtually no serious outcomes are reported for individuals under the age of 19 in the data from China.

Triage
Before seeing the patients at the outpatient department (OPD) or emergency room (ER), it is of utmost importance to assess the possibility of COVID-19 (preferably before arrival at the hospital), as this has consequences for the use of personal protective equipment (PPE), during consultation. In case of suspicion of COVID-19, all medical staff need to be prepared and equipped with PPE, according to the international guidelines.

The majority of patients have mild complaints and will be able to stay at home without an assessment. These patients will be quarantined at home, until fully free of symptoms for at least 1 day. For further advise during quarantine, see the below mentioned treatment advise at home and follow-up.

During triage (preferably on the phone), the following symptoms need to be assessed: new onset of cough, cold, sore throat, (increase in) shortness of breath during rest or with light physical activity, fever*, sudden fatigue*, recent loss of taste and/or smell, gastrointestinal complaints*, headache*, eye complaints indicating conjunctivitis*, muscle and joint pains*.

When an assessment is required, the physician will initially estimate the severity of the clinical situation at the ED or OPD, by triage. If that does not provide sufficient information, physical assessment will be required.

*These complaints make it difficult to distinguish between COVID-19 and other diseases. As an isolated complaint, they are not very specific; however, COVID-19 becomes more likely in combination with other complaints.

Triage at the ED or OPD
In patients with fever, respiratory complaints, gastrointestinal complaints or conjunctivitis, take a medical history, and try to estimate the severity of the clinical presentation.

In case of respiratory complaints, with (suspected) COVID-19, the physician may ask about severe fatigue and exercise tolerance to get an impression of the degree of dyspnea / hypoxemia. Patients with COVID-19 experience relatively few complaints of shortness of breath, whilst they might be undersaturated; fatigue and reduced exercise tolerance may give a better impression of this. Measurements of saturation and other vital signs may help to evaluate disease severity.

In patients with fever without respiratory complaints, try to estimate the possible focus and the severity of the clinical picture.
For gastrointestinal complaints and conjunctivitis, follow those specific guidelines.

4. Management of mild COVID-19: patients who do not require hospitalization

Clinical assessment of patients with respiratory complaints
In urgent situations, the physician uses the ABCDE system.
A physical assessment (for example in case of alarm symptoms) aims to get an impression of the degree of illness.

- Symptoms that may indicate the degree of illness in adults with acute cough are: fever, tachypnea, tachycardia, signs of hypotension, and change of consciousness (confusion, drowsiness).

Specifically, with (presumption of) COVID-19, in addition to the above, oxygen saturation (SpO_2) gives an impression of the severity of the clinical picture. A non-stuffy looking patient with a normal or slightly increased respiratory rate can still have a (very) low oxygen saturation.

Hospitalization is indicated in a critically ill patients, clinically rapid deterioration or if the patient is in need of oxygen, unless otherwise agreed with the patient.

Additional treatment advice at home, in patients with acute cough and suspicion of covid-19

- Uncomplicated respiratory infection;
    - these patients should stay at home during this period until they are free of symptoms for at least 1 day.
- Complicated respiratory infection, this concerns;
    - Patients with a probable pneumonia; start empiric antibiotics according to local protocols, primarily targeting community acquired pneumonia.
    - Patients with risk factor(s) for a complicated course: In these patients, the clinical presentation and comorbidity determine whether or not drug therapy is started.
- Patients with asthma or COPD who experience an increase in symptoms or experience a lung attack, are treated with bronchodilators, inhalation corticosteroids or prednisone orally in accordance with the protocols Asthma in children, Asthma in adults and COPD. This means:

- In case of clinical indications for an exacerbation (wheezing, prolonged expirium, good response to bronchodilators, etc.) also give a prednisone short course, even if COVID-19 is suspected (30mg daily for 7 days/40mg daily for 5 days).
- Consider increasing inhalation corticosteroids (ICS) or increasing ICS / LABA to the maximum dose and adding rescue medication in case of a mild lung attack (mild wheezing, slightly prolonged expirium, minor complaints). (This in the context of restraint with prednisone in (possible) COVID-19).
- If there is no clinical evidence of a lung attack, there is no indication for prednisone.
- There is no reason to discontinue or not to initiate inhalation corticosteroids (ICS).
- If the patient with asthma or COPD has no fever and no signs of pneumonia or severe purulent bronchitis, there is no indication for antibiotics.
- If the patient with asthma or COPD has evidence of a complicated respiratory infection (pneumonia or severe purulent bronchitis), follow the policy for complicated respiratory infection (antibiotics).
- When in doubt (severe asthma, severe COPD, or chronic use of immune modulating medications, such as maintenance dose prednisone and biologicals), consult with a pulmonologist.

Follow-up
It is important to monitor the course in all cases and to contact them in case of deterioration. Patients with a (possible) COVID-19 can still deteriorate even after 8 days (range 5 - 13 days). Advice patients to contact a doctor when there is an increase in symptoms, preferably by phone contact. Consult with the patient how often contact moments are needed.

Consider proactive (daily) contact by phone with patients with suspected COVID-19 belonging to a risk group, at least 7-8 days after the onset of symptoms. This also applies to ill patients who do not belong to the risk group.

Considerations for referral to the hospital
Weigh the following items in vulnerable patients to assess whether hospital admission with possible IC admission has added value.
Consider the limited therapeutic options and the consideration of whether the patient is able to undergo and rehabilitate prolonged ventilation (often 3-4 weeks). There are two guidelines that can assist in the choice of whether or not to send patients in and the further policy.

- Assess the presence of risk factors for a severe course (such as respiratory and lung abnormalities, chronic heart disease, diabetes mellitus, severe kidney disease leading to dialysis or kidney transplantation, decreased resistance to infection).
- "Does this patient have a good chance to recover and rehabilitate to an acceptable functional level if O2 / IV treatment and off-label treatment is given?"
- "Is additional diagnostics necessary to exclude other (treatable) diseases or to estimate the severity of the disease?"
- For admission to IC: "Will this patient manage to be ventilated for 3 weeks in ICU and will he / she be able to go through a long rehabilitation process or is this desirable?"

Additional indications for consultation and referral
In the event of a complicated respiratory infection, consult an internist / pulmonologist, if in doubt about the policy to be pursued, such as for patients from risk groups.

If the patient becomes oxygen deficient (low saturation <92% -94% and / or increased respiratory rate> 24 / minute), or shows clinically rapid deterioration, this is a reason for consultation with a pulmonologist and likely hospitalization. Be careful! Patients are not short of breath, but may have low saturation.

5. Management of severe COVID-19

5.1 Oxygen treatment and monitoring (adult patients)

- *Please make sure you have sufficient and functioning system for supplemental oxygen delivery at your center.*
- *Please refer to the manufacturer's guidelines and instructions for proper and safe use. Oxygen cylinders should be secured and stable so that they could not fall over.*

Supplemental oxygen is the mainstay of care of more severe Covid-19 cases as hypoxemia is very common in those patients. Mild hypoxemia could sometimes even be asymptomatic in otherwise stable Covid-19 patient. To detect hypoxemia, you need a pulse oximeter or arterial blood gas analysis, the latter is generally unavailable in Afghanistan. Using a pulse oximeter, you can measure the oxygen saturation of hemoglobin in the blood (SpO_2).

- *Start immediate supplemental oxygen therapy to patients with respiratory distress, shock or hypoxemia.*

Target SpO2 at 94% or higher during stabilization and resuscitation. Once stabilized, target SpO2 to 90% or higher (>92-95% for pregnant females). Initiate oxygen therapy at 5 L/min flow using a nasal cannula and titrate as needed. Consider using face mask with reservoir bag at 10-15 L/min flow if the patient is in critical condition.
There are various oxygen delivery systems and devices available on the market:

- Nasal cannula with nasal prongs is easy to use and widely available to provide low-flow, up to 5 L/min of oxygen.
- Using simple face masks, the oxygen flow could be increased to 6-10 L/min.
- Face masks with reservoir (non-rebreather) can increase oxygen to 10-15 L/min, 65-95% FiO_2 (concentration).
- High-flow nasal cannula oxygen therapy which involves delivery of heated and humidified oxygen via special devices (eg, Vapotherm, Comfort Flo, or Optiflow), CPAP, and non-invasive ventilation (NIV) systems are generally not available in Afghanistan.
- *Monitor the patient and assess treatment effect frequently and adjust therapy accordingly. Consider complications (for example ARDS, pulmonary embolism, bacterial superinfection, cardiac abnormalities) and act accordingly.*

If the treatment fails intubation and mechanical ventilation, if available, could be initiated. Please refer to the appropriate chapters in this guideline for more details.

5.2 Drug treatments and considerations

In cases of suspected or confirmed COVID-19, the focus should be on supportive care treatment such as additional oxygen therapy and treatment of coinfections. There are no registered/approved therapies available for treatment of COVID-19 and large randomized studies that clearly support the clinical efficacy of a particular drug are lacking. However primary outcomes of a recent study (RECOVERY trial, a RCT) demonstrates beneficial effects of dexamethasone in patients requiring oxygen or mechanical ventilation. Currently, several types of studies are being performed with different possible strategies such as antiviral therapies (Remdesivir), immunomodulatory treatments such as Tocilizumab (interleukin-6 inhibitor), convalescent plasma treatment and development of a vaccine. The efficacy of treatment with plasma is not yet been proven. Given the fact that plasma treatment may be associated with severe complications, we do not recommend this treatment in patients with COVID-19. The latest studies could not find evidence for the efficacy of Chloroquine or Hydroxychloroquine. Therefore, these drugs are no more recommended in the treatment of COVID-19. Based on the current knowledge, not fully scientifically substantiated, the following treatment regimen can be considered in the treatment of COVID-19 patients (Table Management of COVID-19).

Table Management of COVID-19

Confirmed or suspected COVID-19 Disease severity	Possible (drug) treatments	Comments
Mild (patient is stable, no oxygen requirement, no indication for admission).	-No need for PCR. -No treatment. -Instructions for patients. -Consider treatment with (oral) antibiotics to treat a possible community acquired pneumonia (CAP).	-No need for PCR diagnostic. -Choose the treatment for community acquired pneumonia according to current antibiotic guidelines for CAP in Afghanistan.
Moderate to severe (additional oxygen requirement, patient requiring admission in the hospital, risk factors*	-Admission and take protective precautions. -Provide maximum supportive care** - Consider dexamethasone *** -Consider empirically antibacterial therapy. -Start anti-thrombosis prophylaxis ♗	- Consider higher (double) prophylactic dose of LMWH. - Dose dexamethasone: 6 mg daily for 10 days or an equivalent dose of other corticosteroids.
Severe (worsening under initial treatment, indication for intubation).	-Admission and take protective precautions. -Provide maximum supportive care. -In case of clinical deterioration admit patient to the ICU and consider intubation or preferably CPAP (non-invasive ventilation if available). -Start empirical antibacterial therapy. -Start thrombosis prevention therapy ♗ - Consider dexamethasone*** - Consider Remdesivir **** - Consider tocilizumab in patients with signs of HIS and/or ARDS. - Consider low dose methylprednisolone (1 mg/kg) in case of ARDS in later stages of the disease (in the third week).	- Dose anti-thrombosis prophylaxis: double the standard prophylactic dose: e.g. enoxaparin 4000 IU bid. Consider higher doses in patients weighing > 100 Kg. Lower (standard) dose in patients with severe renal insufficiency and/or thrombocytopenia of < 30 x 10^9/l. Use therapeutic doses in case of a (suspected) thrombo-embolic complication if patient has normal thrombocytes. - Dose dexamethasone: 6 mg daily for 10 days or an equivalent dose of other corticosteroids. - Dose Remdesivir: loading dose of 200mg (day 1), thereafter 100mg daily (total duration 9 days). - Tocilizumab dose: 8 mg/kg twice within 24 hours, maximal 800 mg per dose. - Use the Meduri protocol (Chest 2007) for the administration of low dose methylprednisolone for the treatment of ARDS. Beware of bacterial superinfections.

*** Risk factors: underlying cardiovascular diseases, pulmonary diseases, primary or secondary immunodeficiency, use of immunosuppressive, age (>70).**
** **Be careful with excessive intravenous fluid therapy, this may cause deterioration of the ARDS.**
***** Based on recent (16-6-2020) primary results of RECOVERY trial. Note: the study is not published yet. Note 2: this study has only investigated dexamethasone 6 mg once a day for 10 days, the recommendation of using equivalent dose of other corticosteroids as alternative is based on expert opinion of this guideline taking into consideration that in Afghanistan dexamethasone might be scarce and/or sold out. In this case an equivalent dose of other corticosteroids is advised.**
****** off-label use: these therapies should be initiated after informed consent of the patient or the contact persons. The not evidence based use should be discussed. The possible side effects should also be discussed before initiating these therapies.**
♗ **COVID-19 is associated with coagulopathy. Patients are at risk of devel**oping venous thrombotic complications. **Treat patients with prophylactic anticoagulation, unless contraindicated.**

5.3 Treatment of co-infections

Although data are limited, bacterial superinfection does not appear to be a prominent feature of COVID-19. However, since the clinical features of COVID-19 may be difficult to distinguish from bacterial pneumonia, empiric treatment for community-acquired

pneumonia is reasonable when the diagnosis is uncertain and there is a suspicion of bacterial super- or co infection.

Empiric treatment for bacterial pneumonia may also be reasonable in patients with documented COVID-19 if there is clinical suspicion for it (eg, new fever after defervescence with new consolidation on chest imaging, elevated CRP and/or procalcitonin if available).

If empiric antibiotic therapy is initiated, attempt to make a microbial diagnosis (eg, through sputum Gram stain and culture, urinary antigen testing (legionella and pneumococcus)) and reevaluate the need to continue antibiotic therapy daily. It is recommended to start empiric antimicrobials as soon as possible (within 1 hour of initial patient assessment for patients with sepsis).

Empiric antibiotic treatment should be based on the clinical diagnosis (community- acquired pneumonia, health care-associated pneumonia [if infection was acquired in health care setting] or sepsis), local epidemiology and susceptibility data, and national treatment guidelines.

It needs to be addressed that detection of another viral (or bacterial) pathogen does not necessarily rule out SARS-CoV-2 in locations where there is widespread transmission. Coinfection with SARS-CoV-2 and other respiratory viruses, including influenza, has been described, but the reported frequency is variable.

5.4 Acute respiratory distress syndrome (ARDS)

ARDS is a life-threatening lung injury caused by a systemic inflammatory response. The activation of neutrophils causes a sequestration of neutrophils in pulmonary microcirculation, resulting in inflammatory exudate. This edema can cause a serious diffusion disorder with hypoxemia as a result. Patient with ARDS are severely ill and need invasive or noninvasive mechanical ventilation to reach the required oxygenation, see chapter ICU treatment and use of ventilators.

ARDS in patients with COVID-19 is probably the result of a vicious circle of acute alveolar injury due COVID-19 pneumonia, severe hyperinflammation syndrome (HIS) due to cytokine storm and hypercoagulation.

For this document it is important to note that ARDS can be caused by (aspiration)pneumonia but also iatrogenic like mechanical ventilation. ARDS is defined by acute hypoxemia within 1 week in combination with typical radiological findings as (Berlin definition of ARDS).

ARDS and COVID-19 patients
COVID-19 patients with the following characteristics are at risk for developing ARDS: These risk factors are based on a retrospective study done in patients in Wuhan[1]

- Older age (65+)
- Neutrophilia
- Organ and coagulation dysfunction (high LDH, high D-dimer)

- High fever (>39 Celsius)

High fever is associated with higher risk for development of ARDS but is also associated with lower death in COVID-19 patient with ARDS. The other three factors are associated with higher mortality rate.

The development of acute hypoxemia in covid-19 patients is mainly threefold.
1. Due to dysregulation of the pulmonary perfusion,
2. Pulmonary micro-thrombosis, what seems to be one of the main problems of COVID-19 patients due to the hyper-coagulation. The exact pathology and adequate therapy need to be investigated.
3. Most important cause of hypoxemia in COVID-19 patients is pneumonia and pulmonary edema. As described in the chapter radiology, some of the severely ill and hypoxemic COVID-19 patients have relatively less infiltrative consolidations. It seems that pulmonary edema has a prominent role in the development of the 'ARDS-like' clinical findings. We mention here 'ARDS-like' because compared to the classical definition of ARDS you can see that the COVID-19 doesn't fit all the criteria of the Berlin definition (table 1).

It does not fit the timing very well, some of the COVID-19 patients develop ARDS later than within one week of onset; it doesn't fit the chest imaging because the covid-19 chest radiology is heterogeneous (see chapter COVID-19 and radiology). The main criteria that seems to be the same in ARDS and ARDS-like disease is the oxygenation.

<u>Complications</u>
Organ dysfunction such as acute kidney injury, cardiac injury and liver injury is more common in patients with COVID-19 ARDS. Compared with the non-COVID-19 related ARDS there is less sepsis, shock and multi-organ failure in COVID-19 ARDS.
Secondary bacterial pneumonia does not appear to be a major feature in COVID-19 patients. Lung complications such as pneumothorax due to barotrauma is much higher in COVID-19 ARDS. Neurological complications such as delirium or encephalopathy (agitation, confusion and hyperreflexia) are common in critically ill patients. Intensivists have observed that sedation requirements are high in COVID-19 patients, especially after intubation (see chapter ICU).

Recommendations
It is very important to note that data on ARDS in COVID-19 patients are limited. The information in this chapter is mostly based on cohort or case studies.

Pulmonary edema is the main cause of ARDS-like disease, be careful for the complications of ARDS in COVID-19 patients, these are slightly different compared with non-covid-19 ARDS.

6. Management of critical illness and COVID-19: patients requiring ICU admission

6.1 ICU course

The reason for IC admission is generally refractory hypoxic respiratory failure with or without hypercapnia (referred to as ARDS) in 60-70% of admissions, followed by shock (30%), myocardial dysfunction (20-30%) and AKI (10-30%).
Recent data shows that 80% of the Dutch IC population is intubated within 24 hours after admission (58% immediately upon admission). This is comparable to a recent Italian series (n = 1591) in which 88% ultimately required mechanical ventilation. They are also comparable to recent English data, where 81% of patients with advanced respiratory support were intubated in the first 24 hours of ICU admission. In the total IC population (n = 3883) it was only 59%.
The mean IC mortality is approximately 50% (49% in large series n = 2087 from Wuhan, China). Dutch data so far show an IC mortality of 20%, with 54.4% of patients still in IC. This is comparable to the Italian data with 26% IC mortality, with 58% still recorded on IC at the time of publication. Recent English data shows an IC mortality of 50% (based on 1689 of the 3883 patients with full outcome data). The Dutch, Italian and English data are provisional because many patients are currently still in ICU.
The elderly population with co-morbidity in particular has an increased mortality risk (especially> 70 years). Patients may deteriorate further later in the IC course and develop hypercapnic respiratory failure (be aware of pulmonary embolism). In patients who improve, improvement often occurs over a 2-3 weeks period.

Prognostic factors

Unfavorable prognostic factors are: age (> 70); comorbidity: obesity, cardiovascular disease, underlying lung disease, immune suppression, primary or secondary immune deficiency. Also associated with a poor prognosis are: a strongly increased troponin, D-dimer, CRP, and ferritin, a lymphocyte / neutrophil ratio> 3, and further in accordance with normal IC patients, so a high APACHE and more organ failure (increasing SOFA-score).

Respiratory failure and intubation

Until now, the advice has been to intubate early or semi-electively. On the other hand, mechanical ventilation can induce lung damage. In many patients, hypoxemia is at the forefront in the beginning, while there is little evidence of increased work of breathing. The patient often does not feel dyspnea (happy hypoxemia). However, there is a risk that lung disease is underestimated and the patient deteriorates acutely.

HFNC (high-flow /Optiflow) has a place in non-invasive oxygen therapy and can certainly be tried when there are no / hardly any signs of respiratory distress (tachypnea, hypercapnia and / or reduced consciousness). Intubations may be prevented. The signs of respiratory distress should decrease rapidly (within 1 hour).

The WHO (and the NVIC) see High flow as a safe therapy. In the consistent application of the insulation measures (especially FFP2 mask and Glasses), there is adequate protection against the aerosols generated by the flow. Studies in SARS patients seem to show that such

transmission risk is limited and that in particular in aerosol-forming operations, such as intubation and suction care, much more drops are generated than in Optiflow. It is suggested to use the lowest possible flow to avoid any additional spreading.

The application of NIV / CPAP is controversial. Intubations are hardly prevented and patients appear to have a worse outcome after a period of NIV / CPAP in various studies. This may be due to delaying intubation and / or provoking patient self-conflicting lung injury for too long. Also with this therapy there is an increased aerosol formation, which also requires working with FFP2(N95) masks and glasses.

As described above, the findings described in the radiology reports can be very variable, ranging from just some "ground-glass" on CT scan, bilateral interstitial lung image to diffuse lung consolidations with hypoxic respiratory failure. According to L. Gattinoni and colleagues, there is a time-bound disease spectrum with two primary main patterns / phenotypes: The L-phenotype and the H-phenotype. The L-phenotype is characterized, among others, by a preserved lung compliance (low elastance), limited recruitability and a moderate effect on PEEP. This involves low V / Q and reduced hypoxic vasoconstriction. Abdominal position (alternation position) can still be effective by improving the V / Q match. The H-phenotype is characterized by a low compliance with many consolidations on CT scan. These lungs behave more like a "classic" ARDS lung, with a reasonable effect on PEEP and prone position (recruitment). Thus, patients often respond well to prone position and / or sagging independent of the specific phenotype and findings on CT. Most patients will usually present first with an L-phenotype lung and ventilation pattern. During their IC course, a number of patients will develop an H-phenotype lung and ventilation pattern. It is still unclear exactly how this development works and what the role of mechanical ventilation or spontaneous breathing is.

CoVID-19 pneumonia is therefore characterized by a number of aspects:
1. Alveolar edema (ground-glass on CT scan).
2. Atelectasis formation (almost all patients).
3. Two main types have been described:
    a. Viral pneumonitis (L-phenotype): patients with some ground-glass and with some atelectasis formation in the foreground with large shunt over the atelectatic tissue (non-functioning hypoxic vasoconstriction). The remaining lung tissue is relatively spared (A-pattern on ultrasound).
    b. ARDS image (H-phenotype): patients with diffusely affected lungs with areas of ground-glass and a lot of atelectasis / consolidations in some parts of the lung (B-pattern on the ultrasound).
4. Reasonable maintain compliance → low driving pressure (especially in L-type).
5. Patients respond well to high PEEP in diffuse disease. Patients in which atelectasis predominates are at risk of overdistension due to high PEEP.
6. Patients respond well to prone position in both cases.

Circulatory failure

Several hemodynamically relevant complications have been frequently described:
1. Cytokine storm: a distributive shock, often associated with very high CRP and ferritin.

2. Viral myocarditis, characterized by high troponins and occurrence of pump failure and arrhythmias. This often has a refractory course. In the event of circulatory deterioration, it is recommended to perform an ultrasound scan of the heart to assess the existence of heart failure.
3. Arrhythmias: both SVT and VT / VF can occur, sometimes even in the pre-IC course. And they usually respond well to cardioversion / defibrillation. The outcome of CoVID-19 patients who also require chest compressions in addition to defibrillation is usually unfavorable.
Cardiogenic shock due to myocarditis / Takotsubo cardiomyopathy or other sign of multiorgan failure are rarely the cause of IC admission.

Kidneys

Renal impairments requiring CVVH occurs in about 25-30% of ICU COVID-19 patients. Kidney failure is multifactorial: (1) direct damage by virus resulting in endothelial damage, podocytes involvement and acute tubular necrosis, (2) parainflammation by cytokine storm and endothelial dysfunction. In addition, factors such hypovolemia, ARDS, hypervolemia, forward failure by myocardial dysfunction, microthrombi and rhabdomyolysis play an important role in developing acute kidney failure. For more information on pathophysiology, prevention and treatment of renal failure please see appendix 1.

Liver

Mild increase in liver enzymes (especially transaminases) probably due to viral hepatitis is a regular occurrence. Also, medication and hemodynamic instability can play a role in elevated liver enzymes.

6.2 ICU treatment and specific points of attention

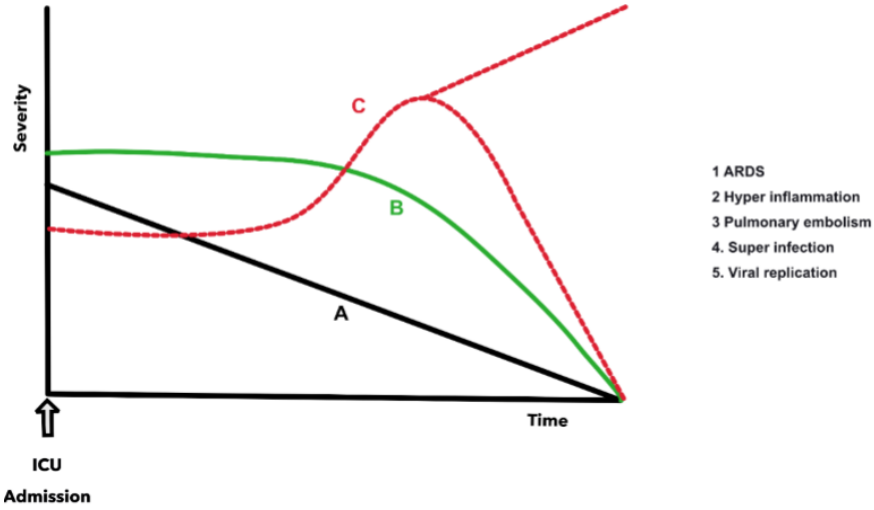
Recently, a lot of theoretical and practical and knowledge has been built up on how best to treat COVID-19 patients. However, many questions remain unanswered, such as: should everyone be intubated equally, how best to ventilate everyone in the different stages of the disease, what is the exact place of anticoagulation, should we use steroids or other anti-inflammatory drugs (such as anti-IL1 receptor blockers, e.g. Anakinra, or anti-IL6 receptor blocker, e.g. Tocilizumab) and if so, at what stage of the disease and at what dose. In addition, not all patients with COVID-19 infection go through the same course of disease and if they worsen, it is based on different, sometimes concomitant, causes. In order to gain some insight into the variation in the course of the disease, we would like to propose a systematic approach in which patients are evaluated at least every 7 days.

Stages in course of COVID infection at ICU

After several weeks of experience, we are discovering that there are differences in the IC course of COVID-19 patients, see figure 1.

After admission to ICU, patients can show an improving trend (group A) or (whether or not after a relatively stable phase) deteriorate (Group B and C). We have learned that there can be several pathophysiological substrates for deterioration. A group of patients worsens

because of increasing atelectasis / ARDS, hyperinflammation, pulmonary embolism, superinfection with bacteria or fungi or perhaps due to failure to control viral replication.



Standardized approach

Below is a summary for the structured approach.

ICU admission

A. Diagnostics

a. CTA to assess lung abnormalities and to identify / exclude pulmonary embolism. Unless CTA is performed in the last 24-48 hours.

B. Treatment

a. Antiviral medication: *Remdesivir*

b. Rest of treatment see below, including:

I. Prevent premature intubation by systematically applying alternation ("awake proning") and Optiflow, especially in "happy hypoxemia" patients.

II. Early intubation in patients with persistent high respiratory drive unresponsive to Optiflow trial.

III. SDD with 4 days Cefotaxim (or alternative).

IV. High dose thrombosis prophylaxis unless pulmonary embolism on CT scan then heparin perfuser with target APTT 60-80 sec and anti-Xa level of 0.3-0.5 IU / ml. Evaluation with CT scan over 7 days.

Day 1-7 of ICU admission

Treatment during this time period is aimed at supporting and, where possible, enhancing spontaneous recovery. In principle, an evaluation of the set policy takes place on a daily basis, where necessary intervention.

A. Diagnostics

a. Cultures (blood and sputum) on indication. Tracheal aspirate twice a week to monitor virus activity and for intensive monitoring of Aspergillus activity. In a positive Aspergillus PCR, a BAL should be performed to distinguish between colonization and actual infection.

b. Daily lung ultrasound

c. CTA only by indication. Exclude pulmonary embolism only at clinical signs of pulmonary embolism (HD instability or increased dead space ventilation). Only the rising D-dimer is not sufficient reason to perform a CTA.

B. Treatment

a. Lung protective ventilation

I. Aimed at low plateau pressure (<30 cmH2O), driving pressure (<15 cmH2O) and Mechanical Power (<30 J / min)

II. Prone position

III. Aim SaO2> 92%

IV. If necessary apply permissive hypercapnia with target pH> 7.25

b. Sedation / pain relief

I. Aimed at accepting ventilation and preventing a high respiratory drive (pressure swings) unless there is a clear improvement in, among other things, the P / F ratio and a lung compliance.

c. Fluid balance

I. Daily goal for negative fluid balance (500-1000 ml / day), unless high fever.

Evaluation every 7 days of IC admission

A systematic evaluation takes place every 7 days if no evident improving trend is observed (improving P / F ratio and / or compliance). You should try to find out which pattern the patient seems to go through (A to C, see figure 1) and which pathophysiological mechanism seems to underlie the possible absence of improvement or deterioration.

A. Diagnosis

a. CTA of the lung

b. Deep lung aspirate: culture, galactomannan and Aspergillus PCR. Corona SARS-2 PCR and culture.

c. Assess trend over time of ventilation parameters, P / F ratio and compliance. Assessment of trend over time of CRP, D-dimer and ferritin.

B. Treatment

Depending on the evaluation above, a specific treatment plan follows:

a. Clinical recovery

i. No action, re-evaluation in 7 days

b. No improvement in P / F ratio, lung compliance or CT findings and no other cause. Consider starting prednisone. Dose and duration of phasing depends on percentage of affected lung tissue and degree of inflammatory activation.

I. Prednisone schedule (adjust duration to clinic)

1 dd 1.00 mg / kg for 7 days
1 dd 0.50 mg / kg for 5 days
1 dd 0.25 mg / kg for 5 days

Further tapering at a guided clinic (5 mg per 5 days)

Cotrimoxazole prophylaxis once daily 480 mg

c. Pulmonary embolism on CTA. Heparin perfuser with target APTT 60-80 sec and anti-Xa level of 0.3-0.5 IU / ml. Evaluation with CT scan over 7 days.

d. New infection

I. Treatment aimed at positive cultures

e. Persistent viral replication

I. Consider Remdesivir

Refractory course or secondary deterioration

After the initiation of initial therapies, a refractory course or secondary deterioration may develop. It is wise to conduct a structured analysis of the most common causes of such a course / deterioration.

Experimental medication

Experimental medication, for the time being especially anti-inflammatory agents / cytokine inhibitors (eg Anakinra / tocilizumab) can be considered in patients with a very predominant hyperinflammatory course (identifiable by a cytokine storm syndrome and strongly elevated ferritin> 5000).

7. Infection prevention and control measures in hospitals

Contact droplet plus (personal protection equipment (PPE) existing of a cap, gown, mask (surgical mask offers sufficient protection), protective glasses or face shield and gloves) is applied for patients with suspected or confirmed COVID-19.

Patients with suspected COVID-19 need to be isolated in single-person room with own bath room. Patients with confirmed COVID-19 may be kept in cohort (group) isolation in a separate ward.

Keep medical equipment and material on the room/ward (do not use these for other patients) until disinfected. Be aware of higher risk of aerosolization (transmission of SARS-CoV-2) during following procedures:

- Non-invasive ventilation and high flow O_2 treatment
- Bronchoscopy
- Intubation
- Nebulization without spacer
- Apply social distancing as much as possible, also in hospitals

Putting on PPE before entering patient's room **(see instructions in your hospital for manners and order of putting on and taking off PPE):**

- Disinfect hands and wrists
- Put on the mask (FFP if available, otherwise surgical mask)
- Put on the face shield (glasses)
- Put on the gown
- Put on the gloves
-

Taking off PPE

- In patient's room:
    - First take off the gloves
    - Take of the gown
    - Disinfect hands and wrists

- Outside patient's room:
    - Take of the glasses (this can be disinfected with hydrogen-peroxide)
    - Take off the mask (see if your center is able to recycle masks)
    - Disinfect hands and wrists

Transporting COVID-19 patient

- Nurse alerts the receiving department and the transport personnel
- State clearly which isolation is the patient in
- Transport the patient with clean clothes and clean linen (in use for max 24 hours ago)
- The patient wears a surgical mask during transport
- Transport personnel: general precautions (ie hand hygiene after contact with patient, bed or wheelchair)
- In case of discharge of a symptomatic patient, patient wears a surgical mask. No company is needed. Instruct the patient to leave the hospital immediately using the shortest route.

Patient measures

- Instruct the patient about good cough and hand hygiene
- Do not leave the room unless for examination or treatment

Visit measures

- No visitors are allowed on the COVID-19 department
- In the other departments, a maximum of 1 visitor per patient is allowed per day, the visitor may enter once. The exception is for terminal patients and children.
- Report to the nurse for instruction on isolation measures
- Visitors wear a surgical mask and apply hand hygiene when leaving the room.

Rooming in of parents / guardians

- No protective measures need to be taken in the room
- Apply hand hygiene after contact with body fluids
- The parent / caregiver should stay in the room as much as possible
- When leaving the room, disinfect the hands with hand alcohol
- When transporting the child, child and parent / caregiver wear a surgical mask
- The parent / guardian may use the facilities in the room

Cleaning / disinfection

- After discharge of a patient with confirmed COVID-19: thorough end-disinfection of the room
- After discharge or transfer of a patient with suspected COVID-19 but result not known yet: thorough end-disinfection of the room
- After discharge of a patient with suspected COVID-19 but negative result: regular cleaning of the room

- Rooms of wards for cohort isolation of COVID-19 patients: daily regular cleaning + disinfection of horizontal surfaces and touch points (door handles, light buttons, etc.)

Measures in the event of patient death
Continue to wear personal protective equipment when caring for (cleaning) the patient and changing the bed. When the patient is ready for transport to the mortuary, the isolation measures can be lifted. The patient does not need to be carried in a body bag.

End / cancel isolation
End isolation only in consultation with the corona coordinator or infection prevention and according to the instructions listed above.

8. Caring for pregnant women, infants and mothers with COVID-19

1. Maternal effects

Pregnant women do not seem to be more sensitive to the effects of a COVID-19 infection than the general population. However, pregnant women with co-morbidity and COVID-19 infection should be taken into account.

Background:
Pregnant women in general appear to be sensitive to respiratory pathogens and severe pneumonia, because of the immunosuppressive state of a pregnancy and the associated physiological adaptive changes (such as diaphragm elevation, increased oxygen consumption and edema of mucous membranes of the respiratory system) which can make them more intolerant to hypoxia.

Given that pregnancy is known to be a hypercoagulable state, and emerging evidence suggests that individuals admitted to hospital with COVID-19 are also hypercoagulable, it follows that infection with COVID-19 is likely to be associated with an increased risk of maternal venous-thromboembolism. Reduced mobility resulting from self-isolation at home, or hospital admission, is likely to increase the risk further.

2. Clinical Symptoms

In pregnant women who develop COVID-19 pneumonia, early data show approximately the same rate of intensive care unit (ICU) admissions as in the non-pregnant population but an increased risk of preterm and cesarean delivery.

Severe sequelae of maternal infection include prolonged ventilatory support and need for extracorporeal membrane oxygenation (ECMO).

A single maternal death from multi-organ failure has been reported in the medical literature, and several anecdotal reports exist.

Clinical symptoms of COVID-19 pneumonia in pregnant women are similar to those in non-pregnant adult women patients with COVID-19 pneumonia.

Hyperthermia, which is common in COVID-19, is a theoretical concern as elevation of maternal core temperature from a febrile illness during organogenesis in the first trimester may be associated with an increased risk of congenital anomalies, especially neural tube defects, or miscarriage; however, an increased incidence of these outcomes has not been observed. Use of acetaminophen in pregnancy, including in the first trimester, has been shown overall to be safe and may attenuate the pregnancy risks associated with fever exposure.

Background:
There are currently no indications that the development of COVID-19 pneumonia in the third trimester of the pregnancy can lead to the occurrence of serious consequences in newborns and fetal infections through intrauterine vertical transmission (Dong et. Al & Zeng et al. JAMA, March 26, 2020).

3. Fetal effects

With regard to vertical transmission (transmission from woman to her baby antenatal or intrapartum), emerging evidence now suggests that vertical transmission is probable, although the proportion of pregnancies affected and the significance to the neonate has yet to be determined. Two reports have published evidence of IgM for SARS-COV-2 in neonatal serum at birth. Since IgM does not cross the placenta, this is likely to represent a neonatal immune response to in utero infection. Previous case reports from China suggested that there was no evidence for this and amniotic fluid, cord blood, neonatal throat swabs, placenta swabs, genital fluid and breastmilk samples from COVID-19 infected women and their babies have so far all tested negative for the virus.

Currently, there are no data indicating an increased risk of miscarriage as a result of a COVID-19 infection. The risk of congenital abnormalities due to the virus is estimated to be highly unlikely. It is unclear whether COVID-19 can lead to spontaneous preterm birth. Fetal distress is described in pregnant women with a proven COVID-19 infection, indicated as most likely secondary due to maternal condition.

4. Neonatal effects

To date, some cases suspected of vertical transmission have been reported in the literature (Dong et.
Al & Zheng et al. JAMA, March 26, 2020). Postpartum horizontal transmission can also take place via an infected contact person. Neonatal case reports of COVID-19 are scarce, however the clinical symptoms in these cases appear less severe.

5. Pregnant women with (suspicion of) COVID-19 and in labor

Suspected COVID-19 should not delay administration of therapy that would be usually given (for example, IV antibiotics in woman with fever and prolonged rupture of membranes).

When the mother gives birth, this is carried out under strict aerogenic isolation measures.

- Mother and child are seen as one, this means both are nursed in strictly aerogenic isolation measures
- There is a minimum distance of 1.5 meters between the beds of the mother and child
- Mother applies cough and sneezing hygiene
- In nursing and breastfeeding, the mother applies hand hygiene and the mother wears a surgical procedure mouth nose mask. (Also see section 8)

6. Mode of birth

- There is currently no evidence to favor one mode of birth over another and therefore mode of birth should be discussed with the woman, taking into consideration her preferences and any obstetric indications for intervention.

- Mode of birth should not be influenced by the presence of COVID-19, unless the woman's respiratory condition demands urgent intervention for birth.
- Where vaginal secretions have been tested for COVID-19, the results have been negative.

8. Recommendations regarding diagnostics

Diagnostics, including radiology, should be performed according to the protocol for the non-pregnant adult. Importantly, the fetus should be protected from radioactive exposure, as far as possible.

8. Neonates born from pregnant mother with suspected or confirmed COVID-19

Normal care post-partum of a healthy a term or premature with gestational age of >32 weeks:
Neonates residing with a positive mother can be cared for by the mother. Also breastfeeding is allowed, if the condition of the mother allows it. When nursing the child or breastfeeding, the mother wears a surgical mask and hand- and cough hygiene is applied. If mother and child reside in the same room, outside the normal mother-child care, there will be kept a distance of 2 meters. Kangaroo care is also allowed if hand- and cough hygiene is applied and the mother wears a surgical mask.

Because of the clear benefits of antenatal betamethasone administration between 24+0 and 33+6 weeks of gestation in patients at high risk of preterm birth within seven days, ACOG continues to recommend its use for standard indications to pregnant patients with suspected or confirmed COVID-19. However, for pregnant patients with suspected or confirmed COVID-19 at 34+0 to 36+6 weeks of gestation and at risk of preterm birth within seven days, the benefits to the neonate are less clear, and ACOG has advised not administering a course of betamethasone to such patients.

Dismissal
If the condition of the suspected or confirmed SARS-CoV-2 / COVID-19 positive mother and child (à term) allows it, it is permissible to strive to dismiss the mother and child back home. The child is staying there in home isolation. If mother and child reside in the same room, outside the normal mother-child care, there will be kept a distance of 2 meters. When nursing and breastfeeding a good hand hygiene is a required and, if available, the use of a surgical mask is advised. Try avoid coughing and sneezing while nursing or feeding the child.

The ill a term neonate or premature with gestational age of <32 weeks:
These patients are neonates with birth defects or premature <32 weeks.

9. Breastfeeding

1. Human milk helps provide protection to newborn infants against many illnesses during early life and is the best source of nutrition for most infants. A limited number of studies suggest that SARS CoV-2, the virus that causes COVID-19, is not detectable in the human milk of mothers with COVID-19 (Chen et al, *Lancet*, 2020).

a) The CDC, WHO, and AAP suggest that the benefits of breastfeeding in the setting of COVID-19 appear to outweigh the potential risks of viral transmission from mother to infant.

2. The following are recommended strategies for the breastfeeding mother-infant dyad with COVID-19:

   a) Mothers who wish to breastfeed directly or pump their breast following birth to initiate lactogenesis, are encouraged to practice excellent hand hygiene and wear a surgical mask during breastfeeding.

      1. When using a breast pump, a dedicated one should be made available to each woman during the postpartum hospitalization.
      2. Breast pumps and components should be thoroughly cleaned in between pumping sessions using standard policies that must include cleaning the pump with disinfectant wipes and washing pump attachments with hot soapy water.

9 APPENDIX 1: Prevention and treatment of acute kidney failure in COVID-19 patients

Multiple dependent pathways in the setting of COVID-19 increase the risk of acute kidney injury (see figure below). The possible hemodynamic, proinflammatory, and proapoptotic consequences of lung inflammation, cytokine release syndrome, and hypercoagulability on renal function, and potential organ support options, are shown.

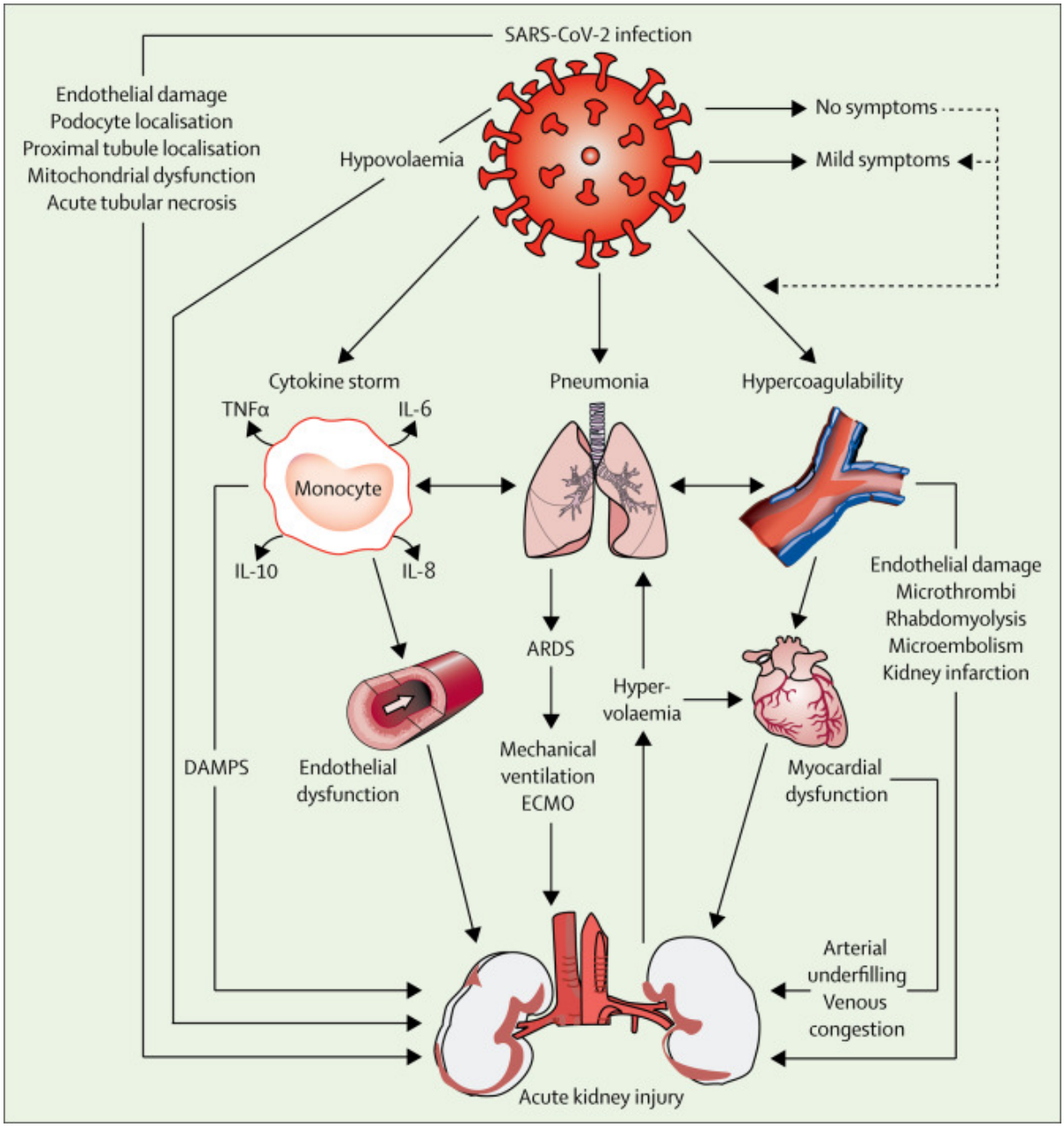


Image taken from original article: "Management of acute kidney injury in patients with COVID-19", Lancet 2020; https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30229-0/fulltext

ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019. DAMPS=damage-associated molecular patterns. ECMO=extracorporeal membrane oxygenation. IL=interleukin. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. TNF=tumour necrosis factor.

Prevention of acute kidney injury (AKI):

- Avoid nephrotoxic medication. This is the only moment that RAS blockers should be terminated.
- Adjust the dosage of antibiotics, daily evaluation is indicated.
- Adjust antidiabetics.
- If possible, avoid iodine contained contrast, for example used for imaging (where applicable). If there is a strict indication for administration of contrast then consider pre-hydration and post-hydration by creatinine clearance lower than 35ml/minute.

Management of AKI in COVID-19 patient:

- Evaluate the volume status of your patient and restore normal volume status to avoid volume overload and reduce the risk of pulmonary edema, right ventricular overload, congestion and subsequently progression of AKI.
- In case of volume overload:
    - Start diuretics: intravenous administration is preferred in case of generalized edema.
    - A Loop diuretic is the first choice, however, the combination therapy with thiazides or potassium sparing diuretics is effective and causes less electrolyte disturbances like hyperNa, hypoK.
    - Start fluid restriction on time!
- If patient with renal failure is volume overloaded and not responding to diuretics then consider dialysis (if available). See below for details.
- Metabolic disturbances secondary to COVID such as hyperkalemia, metabolic acidosis, hypocalcemia and hyperphosphatemia can be treated according to the local guidelines of your center. If not responding to conservative regimen then consider hemodialysis (again, if available).

HEMODIALYSIS (if available in your hospital)

- 4 hours intermittent hemodialysis, 3 times a week seems sufficient also for COVID patients.

▶️ Hemodynamic instability is a limitation for intermittent hemodialysis. If patient is hemodynamically unstable then there is an indication for CVVH, if available at the intensive care unit. As second-best option, consider Slow Low Efficiency Dialysis (SLED). The regular hemodialysis filters and machines can be used for SLED. The duration of dialysis is extended (6 to 10 hours), unstable patients tolerate the low dialysate flow (100 tot 300 mL/min), blood flow of 300mL/minute and slow ultrafiltration better. You can find the protocol for SLED on the following site: https://www.uptodate.com/contents/prolonged-intermittent-renal-replacement-therapy?search=slow%20extended%20daily%20dialysis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

10 References

General sources for uptodate information on infection control, prevention, and treatment guidance:

Source	Title	Link
Infection Control		
European Centre for Disease Prevention and Control	Infection prevention and control and preparedness for COVID-19 in healthcare settings - third update	https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings
World Health Organization	Coronavirus disease (COVID-19) technical guidance: Infection prevention and control / WASH	https://www.who.int/publications/i/item/10665-331495
US Centers for Disease Control & Prevention	Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings	https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html
Collecting PCR VIDEO	NEJM Procedure: Collection of Nasopharyngeal Specimens with the Swab Technique	https://www.youtube.com/watch?v=DVJNWefmHjE
Personal Protective Equipment		
US Centers for Disease Control & Prevention	Using Personal Protective Equipment (PPE)	https://www.cdc.gov/coronavirus/2019-ncov/hcp/using-ppe.html
Public Health England	COVID-19 personal protective equipment (PPE)	https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control/covid-19-personal-protective-equipment-ppe
Treatment		
National Institutes of Health	Coronavirus Disease 2019 (COVID-19) Treatment Guidelines	https://www.covid19treatmentguidelines.nih.gov/
European Centre for Disease Prevention and Control	Vaccines and treatment of COVID-19 *latest evidence*	https://www.ecdc.europa.eu/en/covid-19/latest-evidence/vaccines-and-treatment
World Health Organization pregnancy and childbirth management	Pregnancy, childbirth, breastfeeding and COVID-19	https://www.who.int/reproductivehealth/publications/emergencies/COVID-19-pregnancy-ipc-breastfeeding-infographics/en/

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