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Clinical Management of COVID-19 Patients – An Update

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SARS-CoV-2 virus may cause COVID-19 disease, which causes mild-to-moderate disease in 80% of laboratory-confirmed cases which may be community-managed. A considerable age-dependent mortality is seen among elderly and other at-risk populations but among young and healthy individuals it is < 0.5%. Long-term health issues have been reported following severe COVID-19 requiring hospitalization as well as after cases of mild COVID-19 without hospitalization. Upon receiving COVID-19 suspected patients at hospitals, patients should be isolated and PPE should be worn by all health staff when in contact with the patients. Additionally, patients are tested for the presence of SARS-CoV-2 RNA by PCR, and blood samples are drawn. Imaging is not pivotal for the diagnosis, but chest X-ray is a relevant examination for all and is used to determine severity and treatment need Abnormal findings on CT scans are found in most patients, most frequently peripheral ground-glass opacity and bilateral patchy shadowing are present. Patients are, according to their needs and risks, treated with oxygen therapy, anticoagulation therapy, steroids, antivirals, or immunosupressive drugs on special indications. Convalescent plasma therapy and monoclonal antibodies have a limited role in the treatment, mostly in severely immunocompromised patients. Patients with long-term sequelae should be evaluated in a post-COVID outpatient clinic. The most frequent reported symptoms include cognitive impairment, dyspnea, loss of smell and taste, and mental and physical fatigue although a wide spectrum of symptoms from other organ systems are also reported. The current treatment is based on symptom relief and rehabilitation as there is no documented specific medical treatment.

During 2020-21, a pandemic with more than 160 million cases of the coronavirus disease 2019 (COVID-19) has caused nearly 3,5 million deaths[1] since the first COVID-19 pneumonia was recorded in Wuhan, China, on 31 December 2019.

Clinical studies were initially primarily conducted on hospitalised cases and it was found, that the onset of COVID-19 is associated with symptoms commonly associated with viral pneumonia, most commonly fever, cough/sore throat and myalgia and/or fatigue.[2–3] The initial case definition included a stratification of cases as severe (defined as tachypnoea (≧30 breaths/min) or oxygen saturation ≤93% at rest, or PaO2/FIO2 <300 mm Hg) and critical (respiratory failure requiring mechanical ventilation, septic shock or other organ dysfunction and/or failure that requires intensive care).[4] Initial reports indicated that up to 80% of laboratory-confirmed cases have mild-to-moderate disease and could be community-managed,[5-6] and 14% developed severe disease whilst 6% developed to a critical stage requiring intensive care. The overall case-fatality rates were in early cohorts at 2%-5%,[5-6] overall mortality with the denominator of infected assessed from later surveys of seropositive individuals is lower at 0.5%-1% depending on the age group surveyed.[7] People over the age of 60 years are at highest risk for severe disease and death as well as those with underlying conditions (including hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer).[6] As large-scale testing has become available, it has become clear, that a large proportion of infected individuals are asymptomatic. In

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some studies up to 80%, present with no symptoms when tested but most develop symptoms during the course of the infection, yet up to 30% remain asymptomatic throughout the infection.[8] Long term health issues has been reported following severe COVID-19 requiring hospitalization[9] as well as mild COVID-19 without hospitalization. Long-term symptoms is estimated to occur in 2,5-14 % of people with a positive SARS-CoV-2 result.[10,11]

Receiving COVID-19 Suspected or Confirmed Patients

Patients with suspected COVID-19 include many groups of patients as COVID-19 may present with upper and lower respiratory symptoms but also with general symptoms. Distinct clusters of symptoms have been described: (1) respiratory (cough, sputum, sore throat, runny nose, ear pain, wheeze, and chest pain); (2) systemic (myalgia, joint pain and fatigue); (3) enteric (abdominal pain, vomiting and diarrhoea).[12] However, neither absence nor presence of any sign or symptom have been found accurate enough to rule in or rule out disease.[13]

All COVID-19 suspected patients who are hospitalised should be isolated, and personal protective equipment should always be used by health care staff when in contact with the patients.[14] In order to take into account, the heterogenic nature of clinical presentations, patients with only general symptoms of infection are handled similarly to patients who are admitted with respiratory symptoms.

Diagnosis

Testing for the presence of SARS-CoV-2 RNA is required to confirm the preliminary diagnosis.[15] Test samples are taken from upper or lower airways depending on if a patient shows symptoms involving upper airways, lower airways, or both. From the upper airways, an oro- or nasopharynx swap is made, and from the lower airways, tracheal suction or bronchioalveolar lavage (BAL) is performed. Sampling from the upper respiratory tract requires use of type 2 surgical mask as well as gloves, overcoat and eye protection. Lower airway sampling requires use of FFP2 / FFP3 mask. The diagnosis only requires one positive PCR result for SARS-CoV-2. A negative test result will terminate the isolation unless suspicion remains based on the patient's history, the clinical presentation, blood tests or imaging results. This will lead to new PCR tests as well as broader diagnostic examinations such as sputum for culture, atypical pneumonia and influenza testing. A positive SARS-CoV-2 IgG antibody test is consistent with a previous COVID-19 infection. However, a negative antibody test does not exclude a previous infection, nor does it give any information to whether a patient is protected against a new infection or is infectious.[15] SARS-CoV-2 serology is not therefore used in the acute COVID-19 diagnostics.

Biochemistry should involve hematology including a differential count, inflammation markers such as CRP, procalcitonin and suPAR, renal markers creatinine and eGFR as well as hepatic enzymes with lactate dehydrogenase (LDH) and alanine aminotransferase (ALT). Plasma glucose and HbA1c are measured in all inpatients with COVID-19, and plasma glucose is monitored during dexamethasone treatment. Arterial puncture analysis should be done if there is respiratory distress. Fibrin d-dimer, coronary markers such as Troponin-I and ferritin may be considered in COVID-19 patients due to the risk of cardiovascular events and hyperinflammation. These markers have all been associated with disease progression, severity and outcome.[16,17]

Imaging is not pivotal for the diagnosis, but chest X-ray is a relevant examination for all and is used to determine severity and treatment need. Chest X-rays may be normal, but are often seen with bilateral peripheral interstitial infiltrates. Chest Computerized Tomography (CT) images are not routinely used, but has been used to aid the diagnostic process and determine the need for continued isolation early on in the pandemic when test assays were less sensitive. Manifestations are similar to what is seen in other viral pneumonias and not specific for COVID-19 disease, hence the diagnostic value of chest CT imaging for COVID-19 is low and variable with radiographic interpretation[18] but abnormal findings on CT scans are revealed in more than 80% of hospitalised patients.[19] Another study found that 56% of patients presenting within two days of diagnosis had a normal CT.[20] Frequent manifestations are peripheral ground-glass opacity and bilateral patchy shadowing each found in more than 50% of hospitalised patients.[19] Consolidation is typically seen later in the process.

Treatment

Oxygen and fluid therapy. The main area of focus within treatment options is to maintain an Respiratory Frequency (RF) of <24/min, a SAT_2 above 94%, and/or a pO_2 above 8,5kPa. If the patient fails to keep these levels, oxygen therapy is initiated and is scaled up according to the severity of the respiratory hypoxia. Target levels may vary in patients with comorbidities such as COPD where the habitual $SATO_2$ can be lower than otherwise healthy subjects. A restrictive approach is taken with regard to fluid therapy unless the patient presents with signs of hypoperfusion or shock.[21]

Antibiotics should not be administered routinely to patients with COVID-19 where early co-infection is rare.[22] In case of reasonable suspicion of bacterial infection and need for intravenous treatment, a broad spectrum antibiotics such i.v. Piperacillin / Tazobactam may be initiated or treatment according to microbiological test results.

Anticoagulation therapy. A known and serious condition caused by COVID-19 is a hyperinflammatory response which gives a significantly increased risk of thrombosis in the large vessels (DVT, pulmonary embolism) and in smaller vessels as part of the disease.[23] The pathogenesis for COVID-19-associated hypercoagulability is not clear, but hypothesized to

involve hypoxia and systemic inflammation secondary to COVID-19 which may lead to high levels of inflammatory cytokines and activation of the coagulation pathway.[24] In order to combat this, patients at-risk should have administered Heparin as thromboprophylaxis. In patients where COVID-19 is the primary cause of hospitalization, a daily dosage of Fragmin 5000 ie x 1 should be given, dose reductions apply in case of renal impairment. In intensive care COVID-19 patients, a higher dosage (twice daily) should be given. Active bleeding and a platelet count $<30 \times 10^9$ / L are contratindications of heparin treatment.[25]

Steroid treatment. Dexamethasone should be administered to patients with confirmed COVID-19 pneumonia and in need of oxygen therapy due to hypoxia ($SATO_2$ < 94% without oxygen therapy or lung infiltration on x-ray and in need of oxygen therapy or patients in need of mechanical ventilation or extracorporeal membrane oxygenation (ECMO)). Dexamethason has been shown to reduce mortality among patients in need of oxygen therapy.[26] No effect has been shown in patients without need of oxygen therapy.[27] Daily dosages are 6 mg Dexamethason orally or 8mg Dexavit intravenously in up to 10 days. Pregnant women can as a substitute receive 40 mg Prednisolon a day, 50mg Hydrocortison three times a day or 100mg two times a day. As steroids can promote a reduction in bone density, 400 mg calcium is given with 19 μg vitamin D as supplements two times a day. If steroids are used for more than five days, the supplements are continued for eight weeks unless there are contraindications. Plasma glucose is continually monitored during this treatment.

Antiviral treatment is indicated for patients >12 years old with a COVID-19 pneumonia in need of oxygen therapy but not mechanically ventilated ($SATO_2$ < 94% without oxygen therapy or subjective need of oxygen therapy and lung infiltrations). The viral RNA-dependent RNA-polymerase inhibitor, Remdesivir, has been shown to reduce recovery time as well as mortality in this group of patients within the first 14 days of treatment.[28] The reduced mortality was only found in a subgroup of patients with COVID-19 pneumonia and in need of oxygen therapy, but without the need for invasive mechanical ventilation, within 14 days of starting treatment. No significant effect of Remdesivir has been found in patients without the need for oxygen supplementation, and no effect when initiated in patients already on a ventilator / ECMO. Results from the WHO's SOLIDARITY study found no effect of Remdesivir on risk of death,[29] and WHO does not recommend Remdesivir as part of standard treatment.[30] The optimal duration of treatment in the patient group that has been shown to have an effect of the treatment in the ACTT-1 study is not clear from the currently available data.[31, 32] If a Remdesivir regimen has been initiated before a patient is moved to the Intensive Care Unit (ICU), it should be continued as planned unless signs of side effects occur (eg, increasing kreatinin or plasma alanin aminotransferase (ALAT)). As for immunocompromised patients, data of Remdesivir treatment is lacking. However, based on expert opinion, these patients may draw the biggest benefits of antiviral treatment.[33] Due to the risk of a rapid and fatal outcome, it may be preferable to give Remdesivir as soon as an immunocompromised patient is tested positive for SARS-CoV-2 instead of waiting for the otherwise needed clinical signs before initiating treatment.

Contraindications include an eGFR of <30 mL/minute or dialysis, ALAT >5 times the upper limit of normal levels, hypersensitivity to Remdesivir, multi organ failure, usage of >1 vasopressor drugs, and pregnancy and breast feeding due to lack of data in this area.[34]

Intravenous dosages of Remdesivir is 200 mg the first 24 hours followed by 100 mg daily for another four days. The regimen can be extended another five to ten days for patients with significant Immunosuppression. If patients are discharged before the first five days, treatment is discontinued.

Immunosuppressive drugs. Randomized studies of the interleukin-6 (IL-6) antagonist Tocilizumab for the treatment of COVID-19 have not shown completely unambiguous results. Some RCTs, including COVACTA, showed no difference in mortality on day 28, but several of the studies have shown beneficial effects in terms of reduced risk of progression to need for intensive therapy or death.[35-39] The pragmatic platform studies: REMAP-CAP and RECOVERY included patients who had recently developed a need for intensive therapy, and patients with hyperinflammation and clinical worsening despite treatment with steroids. These studies found slightly lower mortality when treated with IL-6 antagonist (REMAP-CAP, hospitalization mortality: 27% vs 36%; RECOVERY, 28-day mortality: 31% vs 35%).[40,41]

Tocilizumab treatment may be considered in patients with confirmed SARS-CoV-2 infection, age >18 years, immunocompetent, currently in steroid treatment for COVID-19, need of oxygen supply ≥10 L/min in order to keep $SatO_2$ > 92%, CRP >75mg/L, decline in clinical status despite 2 days of steroid or a rapid rise in oxygen demand or initiation of intensive therapy (vasopressor, mechanical ventilation or highflow >FiO2 40% and flow >30l/min) <1 day after admission to the hospital

Relative contraindications are an immune defect, diverticulosis, liver disease or ALAT/ASAT >1,5 times the normal upper level. Absolute contraindications are pregnancy, breast feeding, diverticulitis, ALAT/ASAT above 5 times the upper limit of the normal level, thrombocytes < 50×10^9/L or neutrophiles < 2×10^9/L. Dosages vary according to body weight as 8 mg are given per kilo (up to 800mg) once. Tocilizumab masks super-infections (lack of fever, lack of CRP increase). For patients treated with Tocilizumab, frequent screening should be considered, and a low threshold for microbiological diagnostics applies. Hence, always use procalcitonine instead of CRP, and uphold a low threshold for broad antibiotic treatment. Patients treated with IL-6 antagonist should be offered clinical monitoring as well as control of hematology and liver function

Other antiviral and anti-inflammatory treatment. There is no evidence to recommend other antiviral or anti-inflammatory therapy. Hydroxychloroquine (+/- Azithromycin) and Lopinavir and/or Ritonavir are not recommended for treatment with COVID-19.[29,42-48]

Other antiviral and anti-inflammatory treatment

Baricitinib may reduce the time to clinical improvement by 1 day in patients receiving Remdesivir,[47] but as Remdesivir-treated patients will also receive other immunosuppressive therapy with a proven effect on mortality (dexamethasone), there is not yet sufficient evidence to recommend Baricitinib.

Interleukin-1 inhibitor, Anakinra, is used only under controlled conditions.

Human granulocyte colony stimulating factor has so far not been shown to be effective and is used only under protocol conditions.[48]

Convalescent plasma therapy may reduce the risk of serious COVID-19 pneumonia if given early. Yet, there is no certain effect of giving this treatment among patients already hospitalised with COVID-19.[49-51] Should primarily be used under protocol conditions. Convalescent plasma may be considered in special situations in patients with severe immune deficiency, and may have a place in hospital outbreaks with a known time of infection among patients with risk factors for severe COVID-19 course.

Monoclonal antibodies (mAb) to Spike protein. For 7-10 days after the onset of COVID-19 symptoms, there is active viral replication.[52-54] The amount of virus is higher in people who develop severe or critical illness.[55,56] In few severely immunocompromised patients, especially haematological patients with B-cell defect due to the underlying disease or treatment with anti-CD20 antibody, active viral replication can be detected weeks to months after symptom onset.[57, 58] The same patient population has an increased risk of severe COVID-19. Randomized studies have shown that mAb given to outpatients early in the course of the disease can reduce the relative risk of hospitalization or death by approximately 70%.[59-61] Among immunocompetent individuals, there is no effect if treatment is started only when patients have developed hypoxia and need hospitalization. For severely immunocompromised patients, it is unknown whether treatment is effective among inpatients with COVID-19, as no data from randomized trials are available. There is currently limited access to mAb, and mAb has only preliminary approval in EMA in the form of REGN-COV2 (casirivimab and imdevimab).

Criteria for treatment are: Confirmed SARS-CoV-2 infection by reverse transcription-polymerase chain reaction (RT-PCR) examination of airway sample within 7 days; age $\geq$ 12 years; possibility of starting treatment within 10 days after the first sign of COVID-19 (symptom onset or positive PCR; high-risk patient with haematological malignancy and B-cell defect (primarily lymphoma, CLL, multiple myeloma or treatment with B-cell depleting antibodies within 6 months) or hematological malignancy and recent treatment with high-dose chemotherapy or bone marrow transplantation within 2 years or immunosuppressive treatment for graft-versus-host disease or solid organ transplantation. Vaccinated patients without severe immunosuppression by vaccination should have controlled serology before mAb treatment, and in case of positive serology no mAb should be given. Duration of action is at least 1 month and treatment should not be repeated within this period. There is most often an indication for concomitant treatment with Remdesivir for optimal antiviral treatment.

Discharge

Isolation can be discontinued 48 hours after symptoms have ended or 10 days after debut of symptoms and 48 hours without a fever. Patients after a severe case of COVID-19 should be evaluated individually in regard to the duration of isolation. Immunosuppressed individuals, in particular patients with impaired B-cell function,[57,58,62] may excrete contagious virus for a prolonged time periode, hence ceasing isolation may require expert consultation. Patients can be discharged with or without isolation after recovery of acute symptoms.

Patients With Post Infectious Long-Term COVID-19 Sequelae

There is no internationally agreed definition of long-termCOVID-19 (LTC). Currently COVID-19 signs or symptoms for more than 4 weeks is considered ongoing COVID-19, and signs and symptoms for more than 12 weeks is considered LTC.[63-65] The most frequent reported symptoms include cognitive impairment, dyspnea, loss of smell and taste, and mental and physical fatigue.[9,10,11,66] Life quality is affected, and patients suffering from LTC experience problems performing daily activities and work.[67]

Nerveous System

Early reports describe possible involvement of the central nervous system. However SARS-CoV-2 enchephalits has only been reported in few[68] and stroke does not seem to be more common long after COVID-19.[69] Advanced imaging indicates structural changes in the brain relating to specific symptoms.[70,71] Currently, standard neurological evaluation is recommended when signs and symptoms raise the suspicion of CNS complication or other concomitant disease. MRI or CT of the brain may be needed. Neurophysiological examination has shown signs of myopathy in 11 of 20 consecutively referred patients from a Post COVID-19 Clinic which may explain physical fatigue and muscle aches.[72] As no standard treatment is available for the myopathy clinical suspicion should not nescessarily lead to advances investigations in cases where symptoms are improving (expert opinion).

Cognitive Complaints

More than 60 % of hospitalized patients may experience cognitive problems 3-4 months after hospitalization. Executive functions and verbal learning are some of the areas affected.[73]

It is recommended to use a validated screening tool to evaluate cognitive impairment[64] but a specific screening tool for COVID-19 has not been developed.

Psychiatric Symptoms

Anxiety and depression are more common in the society overall[74] but also more common in patients who had COVID-19 . It has not been established to which extend psychological stress follows the mental and physical long-term effects of COVID-19[75] Attention should be on signs of anxiety, depression or stress when caring for patients with LTC.

Smell and Taste

Smell and taste are affected in more than 10% of SARS-CoV-2 positive patients 6 months after infection.[9] Smell- and taste impairment may improve by using smell- and taste training[76] and in case of lack of improvement the patients should be offered an evaluation by an ear-nose-throat specialist to rule out other pathology and for guidance.

Cardiopulmonary Symptoms

Dyspnoe more than 6 months after COVID-19 has been reported in more than 25% af patietnts hospitalized due to COVID-19[9] and an increased risk was also found in non-hospitalized patients.[10] Only few develop chronic structural pulmonary manifestations like fibrosis – primarily among patients hospitalized in the acute phase of the disease.[67,77] Standard evaluation (spirometry, ecg and chest X-ray) is recommended. Physical tests (like 6 min walk test) may aid the evaluation of patients. Diffusion capacity (DLCO), reversibility test, and pulmonary CT scan may be considered but are not recommended as standard investigation for all patients with LTC. Besides dyspnea, tackycardia heart failure and chest pain was also reported to be more common following COVID-19.[69] The contribution of previous peri- or myocarditis to the long term symptoms has not been established.[78] Currrently arrhythmia, angina and heart failiure should be evaluated according to standard referral criteria.

General Considerations

Post-infectious autoimmune manifestations have been reported,[79,80] and attention should be drawn not to overlook these well-known post viral manifestations in patients who present multiple symptoms. Patients with fatigue, neurological manifestations or dyspnea are recommended biochemical evaluation which may include organ markers (proBNP, liver counts, kidney markers), inflammatory markers, hematology, B12 and folate, thyroid hormones and diabetes screening.

There is no documented specific medication for treating LTC and current treatment is based on symptom relief and rehabilitation. Patientes are observed for improvement during physical rehabilitation and are adviced about mental fatigue. Cognitive therapy guidance concerning mental fatigue and physical rehabilitation is effective in rehabilitation of patients with long-term symptoms following other infectious diseases and seems to be of great importance in patients with LTC (expert opinion). Patients´ guidelines on rehabilitation after COVID-19 has been developed.[81]

A multidisciplinary approach is recommended for patients with multiple symptoms following COVID-19.[63,64] It is important that the clinical evaluation is accompanied by registration, evaluation and research in order hopefully to develop an effective treatment strategy. Outpatient clinics with large numbers of patients suffering long-term symptoms are reported from multipe sites.[82] In Denmark the health authorities recommend that patients with gradually improving symptoms and without need for investigation in hospital are seen in the primary sector. Patients with suspicion of organ specific disease should be evaluated in the relevant speciality. Patients with unexpected ongoing and complex symptoms are recommended referral for a multidisciplinary evaluation.[63]

In summary long-term COVID-19 is a debilitating disease and as numbers of patients with a previous positive SARS-CoV-2 test are still increasing, the human and economical costs are rising. Health politicians should be aware of this planning further preventive measures for COVID-19.

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