

# Clinical Insights and Management Recommendations for COVID-19 Patients Hospitalized in Internal Medicine Departments: Recommendations by the Corona Department Heads in Israel

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The global pandemic of novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), began in Wuhan, China, in December 2019, and has since spread worldwide [1,2]. As of 16 April 2020, there have been more than 2 million reported cases and 135,000 deaths in more than 200 countries, including Israel, which has reported close to 13,000 cases and over 140 deaths [3]. Based on the genetic proximity of the virus, it likely originated from bat-derived corona viruses which spread via an unknown intermediate mammal host to humans. The viral genome of SARS-CoV-2 was rapidly sequenced to enable diagnostic testing, epidemiologic tracking, and future development of preventive and therapeutic strategies [4].

The current understanding of COVID-19 pathogenesis suggests both viral load effect and uncontrolled host immune response. Currently, there is no

evidence from randomized clinical trials that any potential therapy improves outcomes in patients with COVID-19 infection. There are no data supporting any prophylactic therapy [5]. About 400 clinical trials are underway around the world.

In light of this situation, patient management, rather than therapy, should be the goal.

In Israel, COVID-19 patients who are classified with moderate disease (clinical and imaging evidence of pneumonia) are hospitalized in special wards based on the departments of internal medicine that have the capability to treat mechanical ventilated patients.

We suggest a management scheme for COVID-19 patients according to clinical manifestations and current evidence, primarily based on our accumulating experience. Accordingly, current recommendations are expected to change and be updated on a frequent basis.

At these times of uncertainty, the involvement of senior, experienced internal medicine specialists in all clinical and ethical decisions should be encouraged, as well as family support for patients, clinical teaching, and research and collaboration with other medical disciplines and healthcare workers.

## PATIENT EVALUATION [6,7]

Disease severity is dynamic and should be defined daily according to different aspects of disease rather than a comprehensive patient definition. Patients may deteriorate from mild to moderate and severe within hours.

Blood tests should include complete blood count as well as biochemistry including kidney function and liver enzymes such as lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, ferritin, troponin and if feasible interleukin-6 (IL-6) levels. Chest imaging should be included. The frequency of such tests should be individualized to each patient's condition.

The most important risk factors and warning signs for progression to severe disease include advanced age, obesity, diabetes, days since infection [8-15], immune deficiency, clinical evidence for dyspnea and hypoxemia, persistent fever, high NEWS and SOFA scores, increased level of inflammation markers (CRP, IL-6, ferritin), and evidence of hypercoagulability (D-dimer).

All patients older than age 50 years, with a body mass index > 30 kg/m<sup>2</sup>, oxygen room air saturation < 94% or lung infiltrates, or immune suppression should be considered for in-hospital observation for further evaluation.

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Patients with negative polymerase chain reaction but evidence for clinical COVID-19 should be isolated and managed as COVID-19 patients.

#### **PATIENT MANAGEMENT [6,9-10]**

Initial in-hospital management should include measurement of oxygenation, monitoring of respiratory rate, characterization of inflammation level, evaluation of baseline chest X-ray and electrocardiogram, and measurement of troponin level. Empiric treatments should be considered.

#### *IN-HOSPITAL MANAGEMENT ACCORDING TO RISK FACTORS*

All patients with continuous fever, or high respiratory rate, D-dimer > 1000 ng/ml ( $2 \times$  upper normal limit [UNL]), LDH > 500 IU/L ( $2 \times$  UNL), ferritin > 600 ng/ml ( $2 \times$  UNL), or platelets < 100,000 K/mcl should be classified as moderate disease and should be considered for the following treatments. Eligible patients should be incorporated into clinical trials or compassionate care settings.

#### *TREATMENTS CURRENTLY UNDER CONSIDERATION*

The following treatments are currently under consideration:

- Anti-viral medications such as remdesivir and favipiravir
- Anti-IL-6 medications such as tocilizumab and sarilumab
- Hydroxychloroquine
- Convalescence plasma administration

#### *ANTIBIOTIC USAGE*

Patients with high grade fever, alveolar infiltrates on chest X-ray, and elevated CRP during days 9–15 of infection should be considered for treatment with empiric antibiotics for bacterial superinfection (e.g., azithromycin, levofloxacin).

#### *SYSTEMIC STEROID ADMINISTRATION*

Patients at high risk of deterioration (according to the risk factors mentioned) after 5 days (considerable time) in hospital without improvement should be consid-

ered for treatment with systemic steroids (e.g., intravenous methylprednisolone, 62.5 mg/d). Tapering down after 3 days is suggested (e.g., to oral prednisone, 30 mg/d for 5 additional days).

#### *ANTICOAGULATION*

All hospitalized patients should be treated with low-molecular-weight heparin prophylaxis (enoxaparin 40 mg once a day, corrected to glomerular filtration rate) unless there are contraindications. Moderate COVID-19 patients with D-dimer > 5000 ng/ml ( $10 \times$  UNL) should be treated with increased dosage up to 1–2 mg/kg twice a day. Patients with documented thromboembolic events, including deep vein thrombosis, pulmonary embolism, or stroke, should be treated according to regular treatment guidelines.

#### *OXYGENATION AND RESPIRATORY SUPPORT*

All hospitalized patients should be treated with nasal cannula, 3–5 L/minute. If the oxygen saturation with nasal cannula is < 94%, 100% oxygen mask should be introduced and the patient transferred to the intensive care unit (ICU). If the saturation with 100% mask is < 94% use high-flow nasal cannula (HFNC) should be introduced and the patient transferred to the ICU. If saturation with HFNC is < 94% invasive ventilation should be considered and the patient introduced to the ICU.

Awake-prone positioning is recommended for all patients with hypoxemia. Early endotracheal intubation should be considered for frail patients and patients with prominent tachypnea.

#### *DIABETES MELLITUS MANAGEMENT*

Stopping metformin and SGLT2 inhibitors should be considered. Target glucose of 140–180 mg/dl with basal-bolus insulin regimen is preferred. Mild hyperglycemia can be managed with basal insulin  $\pm$  DPP4 inhibitors. For type 1 diabetes or type 2 diabetes on multiple daily insulin injections, application of remote, continuous glucose monitor should be considered.

Stopping angiotensin-converting enzyme (ACE) inhibitors and an angiotensin receptor blocker (ARB) should be considered.

#### *OTHER TREATMENTS, DIAGNOSIS, AND SUPPLEMENTAL MODALITIES*

Folate and zinc supplementation should be considered. Maximal application of telemedicine technologies, assimilated into a clinical-judgment guided management scheme is encouraged.

#### *DISCHARGE*

Patients classified as presenting with mild disease at 14 days of illness should be discharged for further treatment in the community. Suitable patients should be referred to rehabilitation as soon as possible.

#### **CONCLUSIONS**

COVID-19 is a new disease and a major challenge for modern medicine, overwhelming healthcare systems worldwide [11]. Departments of medicine stand at the frontline and lead the medical fight in support of patients with COVID-19. In the absence of evidence-based medicine and approved drugs as well as a lack of previous knowledge and experience, accumulating data collaborative efforts in hospitals around the globe are important but frequently cumbersome. Therefore, experienced clinicians should pause and summarize their insights from time to time.

We believe that the up-to-date accumulated knowledge gathered in Israel could serve our colleagues in Israel and throughout the world. Frequent updates of these insights and recommendations is advisable.

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Capsule

Digestive symptoms in COVID-19 patients with mild disease severity

Coronavirus disease 2019 (COVID-19) most commonly presents with respiratory symptoms, including cough, shortness of breath, and sore throat. However, digestive symptoms also occur in patients with COVID-19 and are often described in outpatients with less severe disease. In this study, Han et al. sought to describe the clinical characteristics, results of stool testing for viral RNA, and outcomes of COVID-19 patients with digestive symptoms and mild disease severity. The authors described a unique sub-group of COVID-19 patients with low severity disease marked by presence of digestive symptoms. These patients were more likely to test positive in stool for COVID-19

RNA, to have a longer delay before viral clearance, and to experience delayed diagnosis compared to patients with respiratory symptoms but no digestive symptoms. In some cases, the digestive symptoms, particularly diarrhea, can be the initial presentation of COVID-19, and may only later or never present with respiratory symptoms or fever. These data emphasize that patients with new-onset digestive symptoms after a possible COVID-19 contact should be suspected for the illness, even in the absence of cough, shortness of breath, sore throat, or fever.

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Capsule

Gut stem cell necroptosis by genome instability triggers bowel inflammation

The etiology of inflammatory bowel disease (IBD) is a multifactorial interplay between heredity and environment. Wang et al. reported that deficiency in SETDB1, a histone methyltransferase that mediates the trimethylation of histone H3 at lysine 9, participates in the pathogenesis of IBD. The authors found that levels of SETDB1 are decreased in patients with IBD, and that mice with reduced SETDB1 in intestinal stem cells developed spontaneous terminal ileitis and colitis. SETDB1 safeguards genome stability, and the loss of SETDB1 in intestinal stem cells released repression of endogenous retroviruses (retrovirus-like elements with long repeats that, in humans, comprise approximately 8% of the genome). Excessive

viral mimicry generated by motivated endogenous retroviruses triggered Z-DNA-binding protein 1 (ZBP1)-dependent necroptosis, which irreversibly disrupted homeostasis of the epithelial barrier and promoted bowel inflammation. Genome instability, reactive endogenous retroviruses, upregulation of ZBP1 and necroptosis were all seen in patients with IBD. Pharmaceutical inhibition of RIP3 showed a curative effect in SETDB1-deficient mice, which suggests that targeting necroptosis of intestinal stem cells may represent an approach for the treatment of severe IBD.

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"Everybody's talking about people breaking into houses but there are more people in the world who want to break out of houses"

Thornton Niven Wilder (1897-1975), American playwright and novelist, winner of three Pulitzer Prizes