NCT
Neumología y Cirugía de Tórax

COVID-19 outpatient evaluation and treatment

Evaluación y tratamiento ambulatorio de la COVID-19

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Abstract

This review article aims to provide an update on the diagnosis and treatment of mild/moderate COVID-19, addressing specific topics such as general recommendations, antiviral treatment, preventive measures (vaccination), and follow-up of patients with long-COVID.

Keywords: *COVID-19 mild/moderate. Long-COVID. COVID-19 treatment.*

Resumen

Este artículo de revisión tiene como objetivo proporcionar una actualización del diagnóstico y tratamiento de la COVID-19 leve/moderada, abordando temas específicos como recomendaciones generales, tratamiento antiviral, medidas de prevención (vacunación) y seguimiento de los pacientes con long-COVID.

Palabras clave: *COVID-19 leve/moderado. Long-COVID. Tratamiento COVID-19.*

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Date of reception: 13-08-2025
Date of acceptance: 29-09-2025
DOI: 10.24875/NCTE.M25000017

Available online: 12-05-2026
Neumol Cir Torax (Eng). 2025;84(2):116-120
www.revistanct.org.mx

Introduction

On December 31st, 2019, the Wuhan Municipal Health Commission (Hubei Province, China) notified the World Health Organization (WHO) of a cluster of 27 cases of pneumonia of unknown etiology, which was later identified as a novel betacoronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2])[1]. Currently, coronavirus disease 2019 (COVID-19) has spread worldwide, causing more than 777 million confirmed infections and nearly 7 million deaths, with an estimated global case fatality rate of 2%, resulting in an economic impact estimated at more than 5 trillion dollars[1,2].

Etiology

The phylogenetic tree of SARS-CoV-2 has shown thousands of viral mutations; however, only 5 have been considered variants of concern: alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529), with its subvariants KP.1, KP.2, and KP.3 (XEK and MC.10.1), the latter currently predominating[3]. The incubation period averages 5 days but may range from 2 to 14 days[4]. After infection, 2 phases have been documented: (1) viral replication, characterized by typical manifestations of upper respiratory tract infection (80% of cases), and (2) inflammatory phase (20% of cases), which may be self-limited or associated with the so-called cytokine storm, progressing to a hyperinflammatory state with severe respiratory and systemic complications requiring intensive care management[5].

Classification of the disease

The clinical spectrum of SARS-CoV-2 infection is highly variable. Four clinical categories are recognized: mild-moderate disease (81%), severe noncritical (14%), severe-critical requiring high-flow supplemental oxygen or noninvasive mechanical ventilation (NIMV), and severe-critical requiring invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) (5%), with possible progression between categories[6,7].

- Mild-moderate disease: the patient maintains oxygen saturation (SpO_2) ≥ 94%, without the need for supplemental oxygen, with clinical manifestations of rhinopharyngitis or laryngitis: sore throat, cough, rhinorrhea, dysphonia, fever, fatigue, headache, myalgias, arthralgias, diarrhea, nausea/vomiting, anosmia, and dysgeusia[8]. Physical examination findings include hyaline rhinorrhea (21%), purulent rhinorrhea (4%), nasal mucosal hyperemia (12%) and edema (3%); pharyngeal hyperemia (39%), hyperemic tonsils (13%), hypertrophic tonsils (2%) with purulent exudates (1%), and lymphadenopathy (4%)[9].
- Severe noncritical disease: SpO_2 < 94%, requiring low-flow supplemental oxygen. Clinical and radiologic evidence of pneumonia is present, including dyspnea, cough, and fine or coarse crackles on chest examination[7].
- Severe/critical disease requiring high-flow oxygen or NIMV: increased dyspnea, cough, persistent fever, and objective signs of respiratory distress with desaturation. Chest imaging (computed tomography) shows extensive lung injury characterized by ground-glass opacities, consolidation, or crazy-paving pattern. Serum inflammatory biomarkers are elevated: interleukin (IL)-6, C-reactive protein, ferritin, and procalcitonin. Hospitalization and intensive care are required[7].
- Severe/critical disease requiring IMV or ECMO: patients with acute respiratory distress syndrome and/or severe sepsis[7].

Of note that some patients may be asymptomatic: individuals with a positive polymerase chain reaction (PCR) or antigen test for SARS-CoV-2 without corresponding COVID-19 symptoms, who may be in a presymptomatic phase and later develop symptoms[5].

Clinical evaluation

Regardless of symptoms, the following considerations should always be identified:

- Time of symptom onset: allows implementation of isolation measures. In immunocompetent patients with mild-moderate disease, isolation continues until the following three criteria are met: (a) at least 5 days since symptom onset; (b) at least 24 hours fever-free without antipyretics; and (c) symptom improvement. In asymptomatic patients, five days from the positive test are considered if no symptoms develop. PCR testing is not required to discontinue isolation in either case[10].
- Warning signs such as dyspnea: some patients develop dyspnea within an average of 5 to 8 days after symptom onset, and acute respiratory distress syndrome has been documented approximately 2.5 days after dyspnea onset[11-13].
- High-risk factors for progression: age (> 65 years, although risk also increases > 45 years, especially with comorbidities), male sex, comorbidities (diabetes, hypertension, morbid obesity, chronic kidney

disease, and chronic obstructive pulmonary disease [COPD])[13], and genetic factors (a cluster of genes located at locus 3p21.31 has been identified as a risk factor for respiratory failure in COVID-19), as well as a probable association with ABO blood group, with higher risk in blood group A[14]. An association has also been described with the G allele of polymorphisms rs4341 and rs4343 related to ACE receptor expression[15].

Management of specific symptoms

Anosmia and dysgeusia are explained by direct damage to olfactory epithelial cells, which may be intensified by central nervous system involvement. Sustentacular and Bowman cells are primarily affected, leading to damage of olfactory receptor cilia and inability to transmit odor stimuli. This damage may be exacerbated by the inflammatory response, leading to pyroptosis[16,17]. Recovery of smell and taste has been described as complete in most cases, with a mean recovery time of 15 (4-27) days after symptom onset[18]. In patients with persistent symptoms, olfactory training has been proposed as the main treatment[19]. Other less common symptoms include sudden sensorineural hearing loss, vertigo, aural fullness, and intralabyrinthine hemorrhage, generally limited to case reports[20]. Additional dermatologic or neurocognitive symptoms may also occur, particularly in older adults[21,22].

Treatment

General measures

Beyond medical therapy, the following recommendations should be emphasized: identify risk factors, classify disease severity, educate patients about warning signs, promote home monitoring, maintain hygiene (bathing and handwashing), follow recommended isolation, ensure balanced nutrition and hydration, and control comorbidities[23].

Symptomatic treatment

In all cases, regardless of severity, symptoms should be controlled with antipyretics, analgesics, antiemetics, and antihistamines[24].

Antiviral therapy

Currently, 2 oral antivirals – nirmatrelvir/ritonavir (Paxlovid) and molnupiravir – and one IV agent (remdesivir) are approved for patients with mild–moderate COVID-19 who have high-risk factors for disease progression. These agents should be administered within the first 5-7 days after symptom onset[7].

First-line therapy is nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days (dose adjustment is required in patients with estimated glomerular filtration rate [eGFR] < 60 mL/min and it is not recommended in those with eGFR < 30 mL/min). Alternatively, if nirmatrelvir/ritonavir is unavailable, remdesivir may be used at 200 mg IV on day 1, followed by 100 mg IV on days 2 and 3 (it should not be administered if alanine aminotransferase exceeds five times the upper limit of normal, and should be discontinued if such elevation occurs)[7,25].

If none of the above options are available, third-line therapy is molnupiravir 800 mg orally every 12 hours for 5 days.

Systemic corticosteroids (dexamethasone), IL-6 inhibitors (tocilizumab), and JAK inhibitors (tofacitinib, baricitinib) are indicated only in severe noncritical and severe-critical cases, as appropriate[7].

Therapies not recommended

Several medications have been studied without sufficient evidence of benefit. Other therapies remain under investigation; however, to date, they are not recommended for the treatment of mild or moderate COVID-19 outside clinical trials. These include azithromycin or other antibiotics, hydroxychloroquine, colchicine, fluvoxamine, supplements (vitamin C, vitamin D, zinc), famotidine, nitazoxanide, antiplatelet agents, anticoagulants (except in the presence of thrombotic risk factors), and ivermectin[7,26,27].

Supplemental oxygen

The use of supplemental oxygen depends largely on altitude. For example, at sea level, an oxygen saturation (SpO_2) ≥ 94% is considered normal; however, at the altitude of Mexico City (2,240 m above sea level), a saturation ≥ 90% may be considered normal. Therefore, the use of supplemental oxygen depends on these reference values. In general, supplemental oxygen is recommended in any patient with SpO_2 < 90% measured by pulse oximetry and should be titrated individually according to patient needs. However, the presence of hypoxemia or the requirement for supplemental oxygen due to COVID-19 without another apparent cause classifies the patient as having severe disease, which is beyond the scope of this article[26].

Follow-up and recovery

Within the first few days of illness, symptoms may present more intensely and persistently. Patients should be advised about variability in total recovery time and symptom duration, which depend on disease severity and prior health status. Moderate disease and the presence of multiple risk factors or comorbidities may prolong symptom persistence for several weeks without implying ongoing contagiousness[28].

Vaccination after acute illness

Vaccination against SARS-CoV-2 should be administered annually, prioritizing individuals at high risk for severe disease. Updated vaccines provide coverage against emerging strains[29].

Long COVID

It is now understood that COVID-19 has an acute course (approximately 1 month), with or without complications, followed by two possible post-recovery states:

- **Post-COVID syndrome:** sequelae occurring in patients who experienced severe COVID-19. Recovery may take 2-6 months.
- **Persistent COVID-19 or long COVID:** a multiple organ symptomatic complex affecting patients regardless of initial disease severity. Patients with mild or moderate COVID-19 may experience persistent symptoms for months, including general symptoms (asthenia, adynamia, diaphoresis, low-grade fever, weight loss, hair loss, insomnia), respiratory symptoms (dyspnea, chest tightness, cough), neurologic symptoms (headache, cognitive impairment with short-term memory loss, vertigo, paresthesias, hyperalgesia, anosmia, dysgeusia), otologic symptoms (hearing loss, tinnitus), cardiovascular symptoms (palpitations, arrhythmias, precordial pain), and gastrointestinal symptoms (nausea, vomiting, diarrhea, hyporexia, hiccups, pyrosis, abdominal distension), among others such as arthralgias, myalgias, and limb edema. Management is complex and requires an interdisciplinary team[30].

Conclusions

COVID-19 is an emerging infectious disease with a case fatality rate of < 2%. It should be classified according to clinical characteristics, including risk factors for progression, symptomatology, physiologic variables (oxygen saturation), laboratory findings, and imaging modalities. Patients with mild-moderate COVID-19 may be treated on an outpatient basis in accordance with recommended therapies.

Acknowledgments

To the National Institute of Respiratory Diseases, for its compassionate care of patients with respiratory illnesses.

Funding

The authors declare that no funding was received.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the drafting of this manuscript.

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