

BOLETIM RAMB COVID-19

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Sars-CoV-2: A clinical update - II

*Mateus da Silveira Céspedes
José Carlos Rosa Pires de Souza*

Em um momento em que há uma emergência mundial de saúde pública, é fundamental que o conhecimento científico gerado durante a pandemia chegue rapidamente à classe médica classe médica.

Dentro desta dinâmica a Revista da Associação Médica Brasileira (Ramb) está adotando uma série de medidas a fim de acelerar o processo editorial para publicação de artigos sobre a Covid-19. A partir de hoje (14/04/2020), a AMB publicará o Boletim Ramb Covid-19, que antecipará os artigos científicos selecionados pelos editores da Ramb sobre o tema.

“Os artigos foram escritos por especialistas e selecionados dentro dos critérios da Ramb para esclarecer temas fisiopatológicos, assim como oferecer orientações de prevenção e tratamento da doença. Dessa forma, esperamos colaborar com os médicos para o melhor atendimento aos seus pacientes, com a disponibilidade mais ágil desses artigos, antes de sua publicação na Ramb”, comenta Carlos Serrano Jr., editor-chefe da Ramb.

Para o diretor científico da AMB, Antonio Carlos Palandri Chagas, “neste momento ímpar vivido no mundo por conta da pandemia de Covid-19, a AMB cumpre seu papel de estar levando à comunidade científica brasileira os recentes artigos sobre os mecanismos fisiopatológicos e aspectos clínicos relevantes dessa situação que assola a saúde pública”.



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Sars-CoV-2: A clinical update - II

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SUMMARY

INTRODUCTION: A covid-19 pandemic decreed by WHO has raised greater awareness of it.

EPIDEMIOLOGY: The infection, reached the mark of 2,000,000 patients in 33 countries and caused the risk of the presence of comorbidities and advanced age.

TRANSMISSIBILITY: The transmissibility calculated so far is similar to the H1N1 epidemic, but with lower mortality rates.

PHYSIOPATHOLOGY: The SARS-CoV-2 virus, of the Coronaviridae family, has the capacity for cellular invasion through the angiotensin-converting enzyme 2 does not have a lower respiratory epithelium and in the cells of the small intestine mucosa.

CLINICAL MANIFESTATIONS: a presentation can be divided into mild (fever, fatigue, cough, myalgia, and sputum) and severe (cyanosis, dyspnoea, tachypnea, chest pain, hypoxemia and need for clinical measurement) and has an estimated estimate of 2%.

DIAGNOSIS: allows the detection of viral load in CRP-TR of patients with high clinical suspicion.

TREATMENT: based on supportive measures and infection control. In severe cases, the use of medications such as hydroxychloroquine and azithromycin or medication can be promising. Take care to avoid the use of corticosteroids. There are no restrictions on the use of resources and IECAs / BRAs.

KEYWORDS: Public health. Coronavirus. COVID-19. Pandemics. Respiratory tract infections. Review.

RESUMO

INTRODUÇÃO: A pandemia de Covid-19 decretada pela OMS suscita maior conhecimento acerca da doença.

EPIDEMIOLOGIA: A infecção atingiu a marca de 2 milhões de pacientes em 33 países e levantou como fatores de risco a presença de comorbidades e a idade avançada.

TRANSMISSIBILIDADE: A transmissibilidade calculada até o momento é similar à da epidemia de H1N1, contudo, com taxa de mortalidade inferior.

FISIOPATOLOGIA: O vírus Sars-CoV-2, da família Coronaviridae, tem capacidade de invasão celular através da enzima conversora de angiotensina 2 presente no epitélio respiratório inferior e nas células da mucosa do intestino delgado.

MANIFESTAÇÕES CLÍNICAS: A apresentação pode ser dividida em leve (febre, fadiga, tosse, mialgia e escarro) e grave (cianose, dispneia, taquipneia, dor torácica, hipoxemia e necessidade de ventilação mecânica) e tem mortalidade estimada de pouco mais de 2%.

DIAGNÓSTICO: Dá-se pela detecção da carga viral no PCR-TR de pacientes com alta suspeição clínica.

TRATAMENTO: Baseado em medidas de suporte e de controle de infecção. Em casos graves, uso de medicamentos como hidroxiquina e azitromicina ou remdesivir pode ser promissor. Deve-se evitar o uso de corticosteroides. Não há evidências suficientes para abster-se do uso de ibuprofeno e IECAs/BRAs.

PALAVRAS-CHAVE: Saúde coletiva. Coronavírus. COVID-19. Pandemias. Infecções respiratórias. Revisão.

INTRODUCTION

Originally discovered in poultry in the 1930s, several coronaviruses cause respiratory, gastrointestinal, liver, and neurological disease in animals. Only seven coronaviruses are known to cause disease in humans. Four of these (229E, OC43, NL63, and HUK1) more often cause symptoms of a common cold. On rare occasions, there may be a severe infection of the lower respiratory tract, such as pneumonia, especially in children, the elderly, and immunocompromised patients¹.

The three coronaviruses that cause the most severe respiratory infections in humans, sometimes even fatal, are considered zoonoses and are described below:

- Sars-CoV-2 is the new betacoronavirus identified on 31/12/2019 as the etiological agent of the disease caused by coronavirus 2019 (Covid-19) described in Wuhan, China.

- Mers-Cov was identified in 2012 as the cause of the Middle East Respiratory Syndrome (Mers).

- Sars-CoV was identified in 2002 as the cause of an outbreak of Severe Acute Respiratory Syndrome (Sars).

It is believed that Covid-19 (Sars-CoV-2) originated in Chiroptera mammals (bats), since they have been reported to a local animal trade in Wuhan, and due to its close genetic similarity to infectious coronavirus in this genre¹.

EPIDEMIOLOGY AND RISK FACTORS

Only 71 days after the discovery of Covid-19 (and 59 days from its genetic sequencing), on 11/03/2020 The World Health Organization declared a pandemic. Thirty-five countries have already registered Covid-19 cases, totaling at least 2 million cases and 115,000 deaths to the date this article was updated. A large global economic

impact has been estimated due to the saturation of health systems and quarantine state, with an expected GDP recession of 30% in the most affected quarter in the US³. Due to the extreme current relevance of the infection and its extension, the writing of this review became necessary to provide medical knowledge and guide the conduct of recently-graduated doctors and others engaged in the fight against this pandemic.

The average age of infected individuals ranges between 49 and 56 years, and the conditions in rare in individuals younger than 20 years (children, in general, are asymptomatic)⁴. Severity increases with age, and the mean age of deaths in Italy (the second epicenter of the pandemic) is 79.5 years.

Among the known risk factors for severe symptomatic presentation are cardiovascular (hypertension) and pulmonary (smoking, asthma) comorbidities and advanced age (over 60 years)⁴.

TRANSMISSIBILITY

Transmissibility is mainly by droplets - close interpersonal contact (less than 2 meters - 6 feet, for a prolonged time) - and fomites⁴. Studies in the USA with 445 contacts of infected individuals found a rate of social contagion of 0.45%. Fecal-oral transmission is possible (due to the presence of ACE2 in the gastrointestinal tract and presence of positive RT-PCR in stool samples), however, it has yet to be documented^{5,6}. There have been reports of intrauterine vertical transmission in the third quarter, with an asymptomatic newborn with increased cytokines and positive IgM⁷.

A very important quantification of viral transmissibility is the basic reproduction number, which is usually denoted by R_0 (pronounced "R-naught"). The epidemiological definition of R_0 is the average number of people who contract a disease from a contagious person. It applies specifically to a population of people who

previously were free of infection and were not vaccinated. There are three possibilities for the potential spread or decline of disease, depending on the value of R_0 :

- If R_0 is less than 1, each existing infection generates less than 1 new infection. In this case, the disease will decrease and eventually disappear.
- If R_0 is equal to 1, the disease will remain alive, but there will be no epidemic.
- If R_0 is greater than 1, the cases will grow exponentially and cause an epidemic or even a pandemic.

As far as we currently know, the R_0 value calculated for 2019-nCoV is significantly greater than 1. The preliminary estimate of a 1.4-2.5 R_0 was presented on the WHO declaration about the 2019-nCoV outbreak on January 23, 2020. Studies had estimated the average R_0 for 2019-nCoV in the initial stage of the outbreak ranging from 3.3 to 5.5 (likely lower than 5, but above 3 with increased rate), which was slightly higher than those of Sars-CoV (R_0 : 2-5), indicating that 72-75% of transmissions must be avoided to stop the growing trend. In contrast, previous studies had suggested that the R_0 for Mers-CoV is less than 1, which means that it is unlikely to cause a pandemic. Super-spreading events have been implicated in the transmission of 2019-nCoV, as was the case with Sars-CoV and Mers-CoV, but its relative importance remains unclear and it is difficult to trace the super-spreaders¹. In addition, R_0 can change seasonally according to climate or annual gatherings¹.

Transmissibility seems to be reduced in hot and humid climates⁸.

PHYSIOPATHOLOGY

Although the reservoir of SARS-CoV-2 animals main remains unknown for a long time, what we have learned so far is that the genomic characterization of the SARS-CoV-2 has shown phylogenetic distance from the coronaviruses previously identified as causes of human diseases; it shared only 79%

and 50% of its identity with SARS-CoV and Mers-CoV, respectively.

Despite these differences, several studies have reported that SARS-CoV-2 explores the same angiotensin-converting enzyme 2 (ACE2) as Sars-CoV to obtain access to its target cells but it presents more binding affinity. It is known that the two main types of ACE can be found in the lung epithelium, and ACE is classically related to the conversion of angiotensin I into angiotensin II, whose effects are vasoconstriction and cardiac remodeling. ECA2, however, is a membrane-bound carboxypeptidase that cleaves a single residue of angiotensin I (Ang I), generating Ang 1-9, and a single residue of angiotensin II (Ang II) to generate Ang 1-7, whose functional effects of vasodilation, anti-proliferation, and antifibrotic oppose those of the Ang II generated by the angiotensin-converting enzyme (ACE). It is known that, by inhibiting ACE (with ACE and ARB antihypertensive drugs), the number of ECA2 in the renal epithelium membrane and in the heart increases, with a theoretical potential of increase in other tissues, increasing infectivity and predisposing to a more serious disease (considering that most critically ill Covid-19 patients were hypertensive, and most hypertensive patients are treated with an angiotensin-converting enzyme

TABLE 1. COMPARISON BETWEEN THE MAJOR CURRENT CONTAGIOUS DISEASES AND COVID-19 REGARDING MORTALITY AND R_0 ¹.

Virus	Fatal Cases (%)	Transmissibility (R)
Covid-19	3	1.4 - 5.5
Sars-CoV	10	2 - 5
Mers-CoV	40	<1
Avian H7N9 (2013)	40	<1
H1N1 (2009)	0.03	1.2 - 1.6
H1N1 (1918)	3	1.4 - 3.8
Rhinovirus	<0.01	6
Ebola	70	1.5 - 2.5
Smallpox	17	5 - 7
Measles	0.3	12 - 18
HIV	80	2 - 4

inhibitor - ACEI or angiotensin receptor blockers - ARB). The presence of cardiomyopathy due to Covid-19 has been demonstrated, with a heart failure prevalence rate in critically ill patients above 40%⁹.

A recent study showed that ACE2 is highly expressed in the mouth and tongue, to facilitate the virus entry into the host. In normal human lungs, ACE2 is expressed in the lower lungs in type I and II alveolar epithelial cells. After infection, the entry of Sars-CoV-2 begins with the binding of the peak glycoprotein expressed in the viral envelope for ACE2 on the alveolar surface. The binding of Sars-CoV-2 to ACE2 stimulates the clathrin-dependent endocytosis of the entire Sars-CoV-2 and ACE2 complex, inducing fusion in the cell membrane. The entry of Sars-CoV-2 endosomal cells is facilitated by endosomal cathepsins, cysteine endosomal proteases of low pH¹⁰.

Once inside the cells, Sars-CoV-2 explores the endogenous transcriptional mechanism of alveolar cells to replicate and spread throughout the lung. Given the critical role of Sars-CoV-2's acid endosomal pH in its processing and internalization, it has been suggested that the antimalarial drug chloroquine could have a potent antiviral effect due to its ability to increase the endosomal pH. From within the cells, chloroquine quickly becomes protonated and is concentrated in the endosomes. The positive charge of chloroquine increases the pH of the organelle by revoking the virus-endosome fusion, ultimately inhibiting the infection. In addition to chloroquine, hydroxychloroquine was considered as a possible candidate for treatment trials in the short term¹¹. In addition, amiodarone has also been suggested as a possible inhibitor of the Sars coronavirus, which spreads due to its ability to interfere in the endocytic pathway¹².

When Sars-CoV-2 infects most ciliated cells in the alveoli. When the normal activity of these cells, which

consists of clearing the airways, is disturbed, there is a consequent progressive accumulation of debris and fluid in the lungs and acute respiratory distress syndrome (ARDS)¹³. There is the possibility of bacterial superinfection, given the aforementioned pathophysiology and the biphasic clinical scenario (evolution to ARDS after 5-8 days of illness).

Since it has been demonstrated that the ACE2-binding affinity is the main determinant of Sars-CoV-2 infectivity, experiments have been carried out at the atomic resolution level of the virus-receptor interaction to identify the precise glycoprotein receptor-binding domain (RBD) of the peak glycoprotein in the viral envelope involved in the Sars-CoV-2 interaction with ACE2. In this study, the author found that the Sars-CoV-2 RBD sequence is similar to that of Sars-CoV, further confirming the hypothesis that ACE2 is the entry receptor for Sars-CoV-2^{10,12}. Notably, it has also been found that the Sars-CoV-2 RBD features a unique mutation that significantly increases its affinity to ACE2 binding, suggesting that Sars-CoV-2 may have evolved with a greater ability to infect and spread among humans.

Although the potential of the aforementioned ACE inhibitors enable a severe clinical picture, *in vitro* studies suggest that the increase of ACE2 attenuates the lung injury caused by Covid-19 infections^{10,13}. There are two main theories for this finding:

- First, the entry of Sars-CoV-2 into the target cells is a regulated, multi-step process, of which ECA2 binding is only the initial step. In fact, TMPRSS2 is an essential serine protease necessary for the glycoprotein peak initiated after the ACE2 binding. The increased expression of ACE2 by ARB could induce the sequestration of Sars-CoV-2 in the cell membrane, which, however, may not be parallel to an increase in TMPRSS2, thus limiting the viral infection. If that is the case, the TMPRSS2 inhibitor,

camostat mesylate, which has been approved for some forms of cancer and hepatitis, can be a valuable treatment option to block various entry routes for Sars-CoV-2. In addition, membrane-bound ACE2 is processed by the metalloproteinase ADAM17, which cleaves the ACE2 ectodomain that can be released in soluble form. Even though ARBs can increase the expression of ACE2 in the lungs, we still do not know whether this also results in an increased rate of ACE2 shedding, which would act as a decoy receptor that reduces Sars-CoV-2 circulation and limits viral entry into the target cells¹³.

- Second, the ARBs allow an increased availability of Ang II by competing with the same AT1R. The increased levels of Ang II become substrates available for the ACE2. The engagement of the ACE2 catalytic domain by its substrates can induce a major conformational change in the three-dimensional structure of this receptor, making it unfavorable to Sars-CoV-2 binding and internalization. In addition, the generation of Ang 1-7 and Ang II by the ACE2 can create a cytoprotective environment in the lungs that can counterbalance the vasoconstriction and profibrotic processes, an important protection mechanism during coronavirus infection, consistent with the protective role of ACE2 in acute lungs¹³.

The aforementioned study and the theories it implies encourage and mitigate the concern of cardiology and nephrology societies about the need to discontinue antihypertensive medication in cases of Covid-19 infection in hypertensive patients.

Studies indicate that the viral load detected in asymptomatic patients was similar to that found in symptomatic patients; however, the viral loads in patients with serious diseases were higher than those of patients with mild to moderate presentations. In addition, higher viral loads were detected in the nasal mucosa than in the oropharynx. This suggests the

effectiveness of an upper swab of the nasal mucosa, which presents less risk to the professional in charge of sample collection¹⁴.

The incubation period ranges from 2 to 14 days (average of 5.2 days). The average time between the first symptoms and the development of acute respiratory distress syndrome (ARDS) is eight days¹⁵. A possible explanation for such rapid and serious deterioration is the cytokine release syndrome (CRS), or 'cytokine storm', an overproduction of immune cells and cytokines, which leads the system of multiple organs to fail and causes fatal damage to the tissues of the lungs, kidneys, and heart.

The current trend to release Covid-19 convalescent individuals from quarantine raises the hypothesis of whether or not reinfection exists. Although other coronaviruses allow reinfection and there have been cases of this process reported in Covid-19, there is no elucidation so far if this is a possibility. Coronavirus infection is known to elicit a short- and medium-term response that suppresses new early reinfections in humans. Research carried out on primates has failed to demonstrate the presence of Covid-19 reinfection¹⁶. Previous data suggest that the IgG for coronavirus peaks in four months and remains positive for three years. However, it is not known whether this conferred immunity is sufficient to provide cross-protection against Covid-19 mutations or other respiratory viruses.

CLINICAL PRESENTATIONS

It is estimated that most individuals are asymptomatic or present only mild symptoms (85%), including fever, fatigue, cough, myalgia, and sputum. There may be anosmia (initial symptom), loss of taste (pre-hospitalization symptom in 91% of patients¹⁷), nausea, headache, emesis, abdominal pain⁶, diarrhea, odynophagia, and rhinorrhea. Severe cases (15%) may include chest pain, dyspnea, cyanosis,

tachypnea, signs of respiratory distress, hypotension, decompensation of underlying diseases, and lymphopenia, and must be treated in a hospital bed. RR >30 bpm, SatO₂ <93%, PaO₂/FiO₂ <300 were indicators of poor prognosis and progression for mechanical ventilation (risk factors for mechanical ventilation: hypertension, diabetes mellitus, and age over 65 years). The mortality rate is around 2.9% (95% CI 1,4-4,3%), lower than SARS (10%)¹⁵. In patients that require intensive care, mortality can be up to 26%¹⁸.

In severely immunosuppressed patients (transplanted), the initial presentation may be gastrointestinal (diarrhea and fever), progressing to respiratory involvement in 48h¹⁹.

A study with dermatologists identified cutaneous manifestations in the course of Covid-19 infection. The manifestations were erythematous rash (14 out of 88 patients), generalized urticaria (3 out of 88 patients), and varicella-type lesions (1 patient). The torso was the main area involved. Pruritus was low or absent, and lesions usually healed in a few days. Apparently, there was no correlation with the severity of the disease²⁰.

A cohort of 99 patients in Wuhan identified changes in liver and canalicular enzymes (GGT, AST, and bilirubin) in up to 54% of patients⁶. The actual meaning of this clinical finding is still unknown. It is known that other coronaviruses do not have the ability to cause encephalitis, and, recently, a case report identified Sars-CoV-2 in a patient's CSF. However, there are no reports yet of neuroinvasive and symptomatic Covid-19 cases²¹.

The most common finding on computed tomography scans of the chest in patients was ground-glass opacity nodules with peripheral and low-lobe bilateral involvement. Such findings may occur even in asymptomatic patients, but are more common in patients with Covid-19-related pneumonia. The presence of a fine fibrotic

layer (fine reticular opacities) indicates a good prognosis of the disease, with progression in remission¹⁵.

Convalescence lasts for one to three weeks for mild cases and from two to six weeks for severe cases²².

DIAGNOSIS

Clinical suspicion is based on the presence of fever and respiratory symptoms (cough, dyspnea). The presence of compatible epidemiology (contact with a suspected or confirmed case, travel to an endemic location in the previous 14 days) increases suspicion of Covid-19 at the expense of other respiratory syndromes and should be an indication for a RT-PCR test¹⁵.

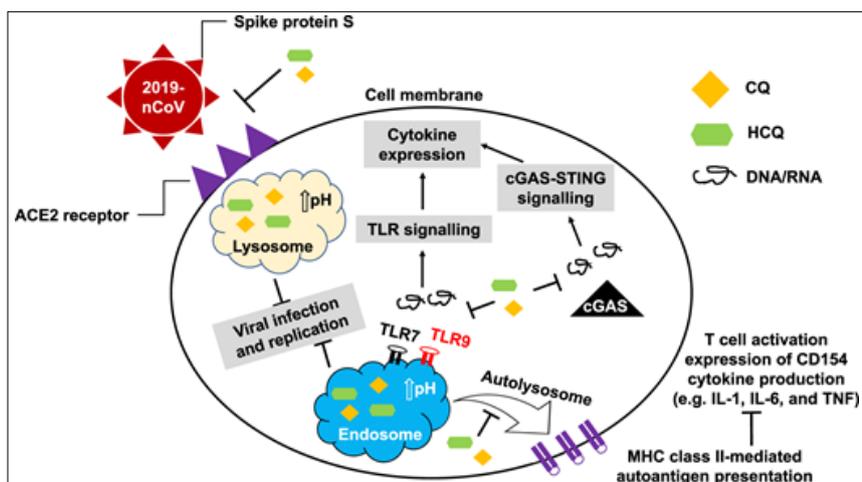
The diagnosis is currently possible only through a positive RT-PCT test. If the test is not available, the presence of high clinical suspicion (compatible clinic signs + favorable epidemiology + blood count suggestive of viral infection) associated with a CT with bilateral peripheral ground-glass opacity pattern of the lower lobes may be sufficient to reach a diagnosis²².

TREATMENT

The treatment is supportive (antipyretics and hydration).

Epidemiological measures of infection control management must be carried out. Mild cases should be treated on an outpatient basis, with home isolation, and instructing all household individuals on sanitary practices (the patient must be restricted to the bedroom, with the door closed and well ventilated, fomites must be sanitized with soap and water or alcohol 70° by the patient, minimal agitation and handling of clothing, frequent sanitation of hands by the patient and other household members, quarantine of all household members for 15 days)². These patients should, ideally, be followed up by the Primary Care team every 48 hours via telephone or teleconsultation. It is recommended to instruct their return if there is a clinical worsening and offer work leave for domestic contacts for 14 days.

FIGURE 1.



Antiviral mechanisms of CQ and HCQ. Both chemicals may interfere in the glycosylation of ACE2 and reduce the efficiency of binding between ACE2 in host cells and spike protein (S) on the surface of the coronavirus. They can also increase the pH of endosomes and lysosomes, thus preventing the process of binding of the virus with host cells and its subsequent replication. When HCQ enters APCs, it prevents antigen processing and the presentation of autoantigen mediated by class II MHC in T cells. The subsequent activation of T cells and the expression of CD154 and other cytokines are suppressed. In addition, HCQ interrupts the interaction of DNA / RNA with TLRs and the nucleic acid sensor cGAS and, therefore, the transcription of proinflammatory genes cannot be stimulated. As a result, the administration of CQ or HCQ not only blocks the invasion and replication of coronaviruses but also mitigates the risk of a cytokine storm.

Severe cases ($\text{SatO}_2 < 95\%$, tachypnea, tachycardia, decompensation of comorbidities) must be hospitalized in isolation, 2 meters away from other suspected cases, and with the necessary precautions. Hand washing and the correct use of PPE by health professionals (gloves, disposable gowns, and N95 masks when entering a room, and caps and face protections during invasive procedures) are indicated, as well as the provision of masks for patients with respiratory symptoms at the hospital reception and in a separate waiting room^{2,14}.

General measures such as oxygen supplementation if SatO_2 is below 94%, hydration, symptom, and decompensated comorbidity control are recommended. Upon medical discharge, the patient must be instructed on possible clinical worsening 5-8 days after the onset of symptoms².

In the case of SBP <90 mmHg, DBP <60 mmHg, or persistence of $\text{SatO}_2 < 94\%$ despite supplementation with a 5l / min nasal catheter, monitoring in an ICU bed and early tracheal intubation is indicated. NIV should be used with caution: although it is

effective in preventing the intubation of patients with respiratory distress, it can cause dispersion of droplets and is indicated for 30 minutes only in a private room with negative pressure. Thus, it is recommended to maintain a negative fluid balance of 0.5-1L/day in case of ARDS, maintenance of the MBP between 65-70 mmHg (in cases of shock, supply isotonic hydration at 30 ml/kg, proceeding to vasoactive drugs if refractory), protective mechanical ventilation (tidal volume 4-8 mL/kg, plateau pressure <30 cmH₂O, PEEP according to the ARDSnet chart), intermittent nocturnal sedation for early weaning, prevention of DVT/PE (stimulate ambulation, use of compression tights/intermittent pneumatic compression, low-molecular-weight heparin), correction of acid-base and hydroelectrolytic disorders, prevention of nosocomial infection (pneumonia associated with mechanical ventilation, infections due to catheters), prevention of decubitus ulcers (change of decubitus every 2 hours) are essential and must be implemented in cases of Covid-19^{2,23}.

Early open and non-random

clinical trials with small samples were promising for use of hydroxychloroquine + azithromycin and remdesivir (antiviral drug developed against the Ebola Virus). Previous results from new randomized studies with larger samples, however, have failed to replicate this efficacy^{25,26}.

Hydroxychloroquine (HQ) and chloroquine (CQ) are immunomodulators implicated in the inhibition of lysosomal activation of antigen-presenting dendritic cells and in the suppression of TLR binding, thus attenuating the production of IL-1, IFN-1, and TNF. The first action would reduce the excessive secretion of cytokines, delaying the overactivation of the immune system triggered by the disease. In addition to this role in modulating the immune response, HCQ and CQ inhibit binding to the receiver and fusion of the membrane, the two main steps necessary for the cell entry by coronaviruses: interfering in the glycosylation of the angiotensin-converting enzyme 2 (ACE2) (the cell receptor of Sars-CoV) and blocking the binding of the virus to the host cell. In addition, they significantly raise the endosomal pH, interrupting the action of proteases and activation of the endosome for virus endocytosis. It is recommended that a dose of 400 mg twice a day of hydroxychloroquine sulfate administered orally, followed by a maintenance dose of 200 mg twice a day for four days. Gastrointestinal responses, such as vomiting and diarrhea are the most common adverse effects of these two drugs. Patients with exposure to CQ exceeding five years suffer severe side effects, such as retinopathy, circular defects (bull's-eye maculopathy), and cardiomyopathy. There is no contraindication to HQ during pregnancy^{11,24}.

Azithromycin, an antimicrobial derived from the macrolide class, has proven in vitro efficacy against the Ebola and Zika viruses^{27,28}. Its mechanism of action against these viruses is not yet fully understood; it acts mainly in inhibiting replication. In addition, it is believed that it can

shorten respiratory viral infection by preventing bacterial superinfections.

The combination of hydroxychloroquine 200 mg 8/8 hours and azithromycin 500 mg in a single daily dose in a French small sample study had encouraging results (70% of viral load clearance with hydroxychloroquine D6 versus 12.5% with the placebo) 23, as shown in the chart below.

Remdesivir is a promising drug along with HQ^{15,29}. Although this antiviral was tested in a study without a control group and with a small sample, it was related to a reduction in the in vitro viral load and a decrease in the severity of the condition. A dose of 200 mg in D1, followed by 100 mg/day for nine days in single daily doses is recommended¹⁵.

The use of corticosteroids has been associated with a worse clinical outcome and is not routinely recommended. Its use in initial presentations was related to a higher viral load, and its use during the period of severe pneumonia was related to delayed clearance of the viral load, as well as the decompensation of diabetes mellitus and the presence of psychosis^{15,19}. However, it should be considered in the presence of septic shock refractory to vasopressors and with suspected adrenal insufficiency.

A recent review that included 11,321 individuals from 14 countries showed that vitamin D supplementation

decreased the risk of acute respiratory infections (ARI) in both those with vitamin D deficiency and those with adequate levels. Specific studies for Sars-CoV-2 are underway to elucidate the real application of these results³⁰.

Measures such as self-quarantine or temperature control at borders should not be very effective since half of the infections are asymptomatic and 44% of the patients do not present fever. Currently, there is a consensus regarding the closing of schools and restrictions of social gatherings (including the closure of workplaces) to limit population movements and introduce the so-called sanitary cordons (quarantines at a cities or region scale). The implementation of these interventions (including sanitary cordons, traffic restrictions, social distancing, centralized quarantine, and universal symptom research) has been temporarily associated with a reduction in the effective number of Sars-CoV-2 infections (secondary transmission) and in the number of confirmed cases per day in groups of age, sex, and geographic regions³¹. There is less consensus regarding which measure should be the first to be implemented, in which combination, and when. The World Health Organization recommends universal testing with subsequent isolation of positive asymptomatic patients (effective measure to control the spread of the virus)¹⁴.

The return to daily activities is still uncertain. It is suggested that, with universal testing, non-transmitting convalescents (IgG positive, PCR-TR negative) may return from isolation and collaborate with the production chain (lockdown reduction). Recently, the World Health Organization suggested the possibility of loosening quarantine for regions with controlled rates of transmissibility, a health system capable of detecting, isolating, and treating all newly infected individuals, control of the risk of imported cases and sanitary control of risk locations (such as long-stay institutions), and a community that is aware and capable of complying with the new standards¹⁴.

It is worth noting that discontinuing ACE/ARB antihypertensive drugs is not recommended due to the potential for cardiac decompensation, as well as the non-use of ibuprofen - when there is no other alternative to this NSAID - is not recommended^{13,15,19}. Passive immunoprophylaxis with convalescent serum in mice has shown a significant reduction in viremia. However, it did not significantly alter the evolution to pulmonary disease³².

DIFFERENTIAL DIAGNOSES IN PEDIATRICS

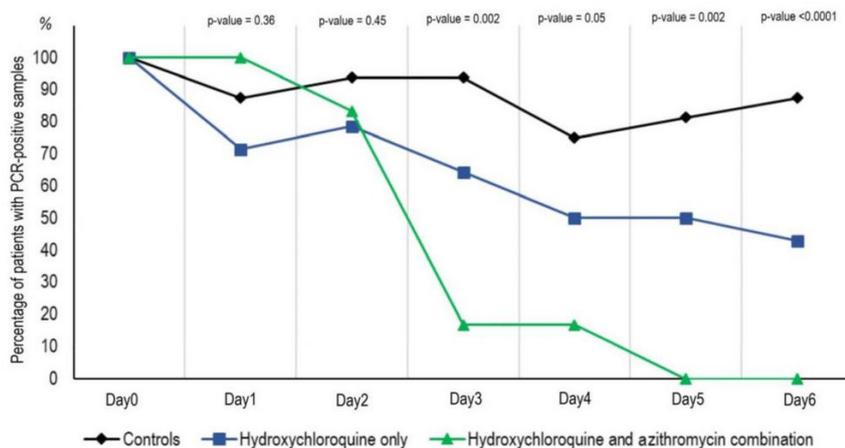
Current data indicate that symptomatic pediatric cases are rare, as are severe cases in individuals younger than 20 years without comorbidities. Thus, faced with a case of pediatric respiratory syndrome, one of the differential diagnoses below should be considered:

Acute viral rhinopharyngitis

It is the most common infectious disease during childhood (children younger than five years usually present from five to eight episodes per year)^{33,34}.

The most common etiologic agents are rhinovirus, coronavirus, respiratory syncytial virus (RSV), influenza, parainfluenza, coxsackie, and

CHART 1. COMPARISON OF VIRAL CLEARANCE WITH A PLACEBO, HYDROXYCHLOROQUINE, AND AZITHROMYCIN23



adenovirus. The transmission is by droplets and direct contact with the mucous membranes, and the incubation period is of 2-5 days. The affected individual presents a risk of contagion in the one-day period before the onset of symptoms and two days after it.

The clinical presentation lasts from five days to seven days and includes rhinorrhea, nasal obstruction, dry coughing, sneezing, pharyngitis, and fever of variable intensity. There may be hyperemia of the tympanic membrane, changes in sleep, and irritability in infants. The adenovirus and RSV may generate lower airway infection (leading to tachypnea, retractions, and grunting). The influenza virus is implicated in a more severe clinical presentation, with diarrhea, abdominal pain, prostration high fever, and myalgia, which puts the clinical presentation of a common cold (coryza, nasal obstruction, cough, and pharyngitis) in the background. Both RSV and rhinovirus can trigger asthma episodes^{34,35}. There may be complications with acute otitis and sinusitis due to the obstruction of the ostia of the paranasal sinuses and eustachian tube, secondary to the inflammatory process or indiscriminate use of decongestants.

The diagnosis is clinical and should be differentiated from hepatitis A (onset of jaundice, increased direct bilirubin and transaminases), measles (intense cough, conjunctivitis with photophobia, exanthema, and enanthema of koplik), pertussis (severe cough, and may cause vomiting and dyspnea, duration of six to ten weeks, absence of vaccination), rhinitis (AURTI caused by winter, positive family history and personal history of atopy, remission after use of nasal corticosteroids), streptococcal pharyngitis, and mononucleosis (both with intense hyperemia of the oropharynx, petechiae on the palate, hypertrophy of the tonsils and purulent plates). The detection of the virus is unnecessary.

The treatment consists of rest

during the febrile period, nasal instillation of isotonic saline solution (3-5 mL in each nostril every 2 hours), and antipyretic medication. In adults with influenza A, one can resort to amantadine 200 mg every 24 hours (pre-contact prophylaxis with 70-80% of effectiveness, equally effective treatment with a reduction of the symptomatic period)³⁴. In children older than 12 years or weighing over 40 kg and adults with suspicion of influenza type A or B, oseltamivir 75 mg can be used every 12 hours for five days (pre-contact prophylaxis with 92% efficiency, reduces the severity and duration of symptoms, can be used in children over 1 year)³⁴. The use of probiotics and vitamin C in high doses (>1g/day) has proven effective in the prevention of rhinopharyngitis in athletes, as well as in the reduction by 20% of the duration of the condition in children. Caretakers should be instructed on the need for hand hygiene at home and to return in case of clinical worsening.

Acute sinusitis

Defined as a bacterial infection of the paranasal sinuses, with a duration of fewer than 30 days. Acute sinusitis is rare in small children since the maxillary and ethmoidal sinuses are reduced before the age of 2 years, and the frontal and ethmoidal sinuses develop from the age of 4 years^{34,35}.

The most frequent etiological agents are *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*³⁵.

Acute sinusitis is suspected when there is the persistence of AURTI exceeding ten days or recurrence after clinical improvement. The symptoms include nasal obstruction, purulent rhinorrhea, halitosis, coughing with worsening at night, fever, and frontal tension headache (may also present as pain in teeth). There may be osteomyelitis, periorbital cellulitis (a sign of ethmoiditis), meningitis, thrombosis of the cavernous sinus, and brain abscess.

The diagnosis is clinical and an x-ray of the paranasal sinuses is usually unnecessary. It must be differentiated from adenoiditis (snoring, epistaxis, acute otitis media) and nasal foreign body (obstruction and asymmetrical rhinorrhea, history of foreign body insertion). It may be necessary to have a specialized assessment if sinusitis lasts for over 90 days or in case of recurrent sinusitis. It may be necessary to have a computed tomography of the skull in refractory cases or in case of suspected complications³⁴.

The treatment consists of rest, antipyretics, nasal instillation of isotonic saline solution every 2 hours, topical or systemic corticosteroids (in case of a history of asthma), and antimicrobial agents. The first choice is amoxicillin clavulanate 875+125 mg every 12 hours for seven days (or ten days in case of resistance factors)³⁴. Other options are cefuroxime, clarithromycin, or azithromycin. In the absence of a response after 48 hours, consider doubling the dose or changing the medication. Instructions to avoid decongestants and diving during periods of AURTI, avoid smoking (active and passive), and proper treatment of allergic rhinitis.

Children with allergic rhinitis can present chronic or repetition sinusitis³⁵.

Streptococcal pharyngitis (SAP)

SAP is an acute infection of the oropharynx by *Streptococcus pyogenes* (group A beta-hemolytic). It is transmitted via droplets or direct contact with patients, presents incubation of two to five days, and represents 15% of AURTI^{34,35}.

The most common clinical presentation is high fever, odynophagia with sudden onset, pharyngeal hyperemia, hypertrophy of the tonsils and tonsillar exudate, associated or not with prostration, cervical adenopathy, vomiting, and abdominal pain. It can complicate with cervical lymph node abscesses, acute otitis media,

post-streptococcal glomerulonephritis, reactive arthritis, rheumatic fever, and sepsis³⁵.

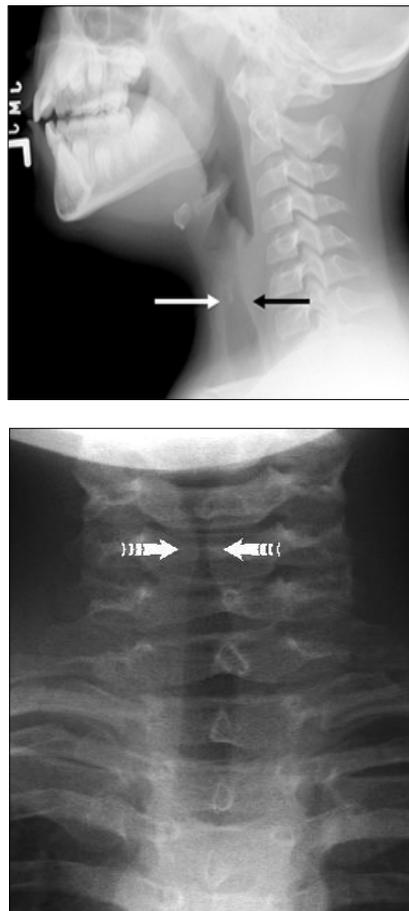
The diagnosis is clinical, and a quick test can be used. It must be differentiated from scarlet fever (strawberry tongue, exanthema with signs of Pastia - increase of the flexural exanthema, and Filatov - perioral pallor), viral pharyngitis (coryza, absence tonsil hypertrophy, and exudate), diphtheria (predominant diarrhea, grayish-white plates in the oropharynx that may invade the uvula) and infectious mononucleosis (generalized adenopathy, exanthema after the use antimicrobial agents)³⁵.

The treatment is based on rest, instillation of warm saline solution in the oropharynx, antipyretics, and antibiotics (the drug of choice is benzathine penicillin G 600 thousand or 1.2 million IU IM single dose, for <27 kg and >27 kg, respectively)³⁴. The treatment is less painful if a heated solution used for dilution. In the case of allergy to penicillin, the drug of choice is erythromycin estolate 40 mg/kg/day in 2-3 administrations. Instruct the patient to return in case of dysphagia and muffled/nasalized voice (tonsillar abscess), dyspnea, exanthema, or clinical worsening. Instruct to be absent from nursery/school and work activities for 48 hours after starting the treatment³⁵.

Viral croup

This is subglottic laryngitis, a viral infection with a variable degree of congestion and obstruction of the airways. It is often caused by RSV

FIGURE 2. CERVICAL RADIOGRAPHS THAT ARE SUGGESTIVE OF VIRAL CROUP. IMAGE BY JOHN MCBRIDE, MD.



and parainfluenza I and II, presents a natural history of partial obstruction of the airways for 2-3 days, with remission after five days³⁵.

Clinical manifestations include prodromes (runny nose, dry cough, nasal obstruction, and fever) and frank laryngitis (hoarse cough, dysphonia/aphonia, and inspiratory stridor). There may be signs of respiratory failure (nasal flaring, subcostal

retraction, tachypnea, cyanosis/pallor) and progression to airway obstruction and death.

The diagnosis is clinical and can be aided by radiography (laryngeal narrowing with pencil-point sign). It must be differentiated from a foreign body (sudden onset of airway obstruction, with cyanosis and cough), a congenital malformation of the airway (repeat laryngitis), spasmodic laryngitis (absence of prodromes, nocturnal onset, spontaneous regression, personal history of GERD, and improvement with humidification) and allergic laryngeal edema (history of exposure to allergens or drugs, presence of angioedema, and other stigmata of anaphylaxis)³³.

The treatment is based on the humidification of the environment and hydration, as well as symptomatic treatment. In severe cases (progressive or at rest stridor, signs of respiratory failure, toxemia), use inhaled corticosteroids and consider tracheal intubation³⁵. ■

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REFERENCES

- Chen J. Pathogenicity and transmissibility of 2019-nCoV: a quick overview and comparison with other emerging viruses. *Microbes Infect.* 2020;22(2):69-71.
- Brasil. Ministério da Saúde. Protocolo de manejo clínico para o novo coronavírus (2019-nCoV). Brasília: Ministério da Saúde; 2020. [cited 2020 Abr 4]. Available from: <https://www.saude.gov.br/images/pdf/2020/fevereiro/11/protocolo-manejo-coronavirus.pdf>
- The New York Times. Morgan Stanley to Buy E-Trade, Linking Wall Street and Main Street. Access in 24/03/2020.
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020 Feb 7. doi: 10.1001/jama.2020.1585.
- Tang A, Tong ZD, Wang HL, Dai YX, Li KF, Liu JN, et al. Detection of novel coronavirus by RT-PCR in stool samples from an asymptomatic child, China. *Emerg Infect Dis.* 2020;26(6):10.3201/eid2606.200301. doi:10.3201/eid2606.200301.
- Wong SH, Lui RN, Sung JJ. COVID-19 and the digestive system. *J Gastroenterol Hepatol.* 2020 Mar 25. doi: 10.1111/jgh.15047.

7. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. *JAMA*. 2020 Mar 26;e204621. doi: 10.1001/jama.2020.4621.
8. Wang J, Tang K, Feng K, Lv W. High temperature and high humidity reduce the transmission of COVID-19 (9 March 2020). [cited 2020 Abr 2]. Available from: <https://ssrn.com/abstract=3551767>
9. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. 2020 Mar 30;NEJMsr2005760. doi: 10.1056/NEJMsr2005760.
10. Ye M, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. *J Am Soc Nephrol*. 2006;17(11):3067-75.
11. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother*. 2020. doi: 10.1093/jac/dkaa114.
12. Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen KY. Coronaviruses: drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15(5):327-47.
13. Perico L, Benigni A, Remuzzi G. Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade. *Nephron*. 2020 Mar 23:1-9. doi: 10.1159/000507305.
14. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. January 25, 2020. [cited 2020 Abr 2]. Available from: [https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-\(ncov\)-infection-is-suspected-20200125](https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125)
15. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths. *J Microbiol Immunol Infect*. 2020. doi: 10.1016/j.jmii.2020.02.012.
16. Bao L, Deng W, Gao H, Xiao C, Liu J, Xue J, et al. Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. [cited 2020 Abr 4]. Available from: https://www.biorxiv.org/content/10.1101/2020.03.13.990226v1.full.pdf?_cf_chl_jschl_tk_=42279e7e91e54436edfb79a91e859c052bcb4b4b-1587324744-0-AUWJQ1noKeEJ6jBzPbPKsEYwgmI9P3UBZiNj34WO2AfK2aaWeJyJEna-ykMNM-Gzy276L4hC7achngwceyu0mSbf77Qiw92JRxvgrjIUf2eZNV4GmQLtMl2kcFR0VeqAjSZux-JE6yb-qOibMlPeLtCq9DMh1tv6SlGvGpoXbhjNVXtG1KCbykp-16h61unHWUUmDjYykMwuUeksuaelnhE-nXKwE3o28zEcNesMh2DtEGGjG5_3_Apdcawhl05E-KWT5NluX1gl8n4zIOLZTvZOOYUUDLk3K176QpjOz_LKHWY522AHyamdxYrF203iHuL-PgPZwEALsLGM-4_bc
17. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. 2020;ciaa330. doi:10.1093/cid/ciaa330
18. Grasselli G, Zangrillo A, Zanella A, Massimo Antonelli, Luca Cabrini, Antonio Castelli, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020 Apr 6;e205394. doi: 10.1001/jama.2020.5394.
19. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020. doi: 10.1016/S2213-2600(20)30079-5.
20. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020 Mar 26. doi: 10.1111/jdv.16387.
21. Sun T, Guan J. Novel coronavirus and central nervous system. *Eur J Neurol*. 2020 Mar 26. doi: 10.1111/ene.14227.
22. Burke RM, Midgley CM, Dratch A, Fenstersheib M, Haupt T, Holshue M, et al. Active monitoring of persons exposed to patients with confirmed COVID-19 - United States, January-February 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(9):245-6.
23. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet Respir Med*. 2020;2600(20)30127-2. doi:10.1016/S2213-
24. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020. doi: 10.1093/cid/ciaa237
25. Multicenter Collaboration Group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for Chloroquine in the Treatment of Novel Coronavirus Pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;43(0):E019.
26. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72-3.
27. Retallack H, Di Lullo E, Arias C, Knopp KA, Laurie MT, Sandoval-Espinosa C, et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. *Proc Natl Acad Sci U S A*. 2016;113(50):14408-13.
28. Madrid PB, Panchal RG, Warren TK, Shurtleff AC, Endsley AN, Green CE, et al. Evaluation of ebola virus inhibitors for drug repurposing. *ACS Infect Dis*. 2015;1(7):317-26.
29. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med*. 2020 Apr 10. doi: 10.1056/NEJMoa2007016.
30. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017 Feb 15;356:i6583. doi: 10.1136/bmj.i6583.
31. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. *JAMA*. 2020 Apr 10;e206130. doi: 10.1001/jama.2020.6130.
32. Chan JFW, Zhang AJ, Yuan S, Poon VKM, Chan CCS, Lee ACY, et al. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. *Clin Infect Dis*. 2020; ciaa325. doi:10.1093/cid/ciaa325
33. Goldman L, Schafer AI. *Cecil medicina interna*. 24ª ed. Rio de Janeiro: Elsevier; 2012.
34. Pitrez PMC, Pitrez JLB. Infecções agudas das vias aéreas superiores: diagnóstico e tratamento ambulatorial. *J Pediatr*. (Rio J.) 2003;79(Suppl 1):S77-S86.
35. Behrman RE, Jenson HB, Kliegman R. *Nelson tratado de pediatria*. 19ª ed. Rio de Janeiro: Elsevier; 2013.