REVIEW

General aspects of the COVID-19 pandemic

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Abstract

Objectives: to review the available literature on the general aspects of SARS-CoV-2 infection.

Methods: this is a narrative literature review carried out from March to September 2020.

Results: COVID-19 caused by the new coronavirus or SARS-CoV-2, grows with devastating effects worldwide. The literature describes epidemiological data and mortality risk groups of the disease, which presents a high rate of transmission. Prevention is the most effective way to fight the disease, persisting the absence of strong evidence on the treatment. Vaccines are not yet available. Dexamethasone is effective in reducing mortality in severe forms.

Conclusions: despite great efforts, as the number of confirmed cases increases, evidence on transmission, incidence, disease progression, lethality, effects and outcomes remain limited and without any high levels of evidence. Studies are still necessary for all aspects of the disease.

Key words *Coronavirus, COVID-19, Coronavirus infections, Severe acute respiratory syndrome, Coronavirus 2, SARS-Cov-2,Gestation, Maternal mortality, Perinatal mortality*

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http://dx.doi.org/10.1590/1806-93042021005100003

Introduction

Since the end of 2019, the world faces a crisis after the discovery of a new virus. This virus is a variation of a pre-existing coronavirus, called new coronavirus (SARS-CoV-2) a disease that causes predominantly respiratory manifestations. The first study that demonstrated some of the manifestations of this virus on humans was published in January 2020.[1,2]

This disease is considered a zoonosis, an infection naturally transmissible between vertebrate animals and humans, whereas non-ill animals harbor and eliminate the etiological agents. The animal in which the disease originated is still being investigated. It has been speculated, based on the genetic sequencing of the virus, that bats or even pangolin, a mammal of the *Manis Javanica* species, are the most likely to be the origin.[3]

On December 31, 2019, the World Health Organization (WHO) was informed of pneumonia cases of unknown etiology detected in the city of Wuhan, province of Hubei, China,[4] and later recognized as an infectious disease caused by the new coronavirus (COVID-19). This city, at first, was considered the world epicenter, surpassed by Italy, which quickly accumulated more cases and deaths.[3,4] It is speculated that the first case of the new coronavirus appeared on November 17, 2019, and that it would have been a 55-year-old man, resident in the province of Hubei.[5]

France was another country quite affected. A study suggested that the virus was circulating in France approximately 30 days before the official cases were registered. It was a 42-year-old Algerian man living in France and a fishmonger, that on December 27, 2019, reported having hemoptysis, cough, headache and fever for four days. Computed tomography revealed bilateral frosted glass opacity in lower lobes and the Reverse transcription polymerase chain reaction (RT-PCR) examination for SARS-CoV-2 was performed, retrospectively was positive.[6]

Due to the increased number of cases in China and other countries, WHO, on January 30, 2020, declared to be an international public health emergency. On March 11, 2020, a pandemic was declared and all the countries in the world had to make contingency plans.[7]

To have an idea of the speed of the contamination and the seriousness of this virus, there were 760,040 cases and 40,842 deaths in the world on March 31, 2020, with an increase, after six months, on September 27, 2020, to 32,925,668 confirmed cases and 995,352 deaths.[8]

With the growing number of infected people and deaths, the epicenter of the disease was rapidly changing from China to Italy, Spain, and the United Kingdom, sequentially, and in the months of April and May to the United States of America (USA), where the number of cases exceeded all countries. In Brazil, on September 28, 2020, reached 4,745,464 cases and 142,058 deaths, staying behind the USA.[8,9]

Nomenclature

WHO, on February 11, 2020, established the official nomenclature, when the virus was called coronavirus-2 of severe acute respiratory syndrome (SARS-CoV-2) and infectious coronavirus-19 disease (COVID-19).[10]

Etiologic Agent

The coronaviruses were first described in the 1960s, they are the largest single strand of ribonucleic acid (RNA) virus, spherical, encapsulated and surrounded by a layer of proteins. The *S* protein, a specular aspect, produces a crown-like structure, determining the virus tropism and fusion with the host cells. They belong to the Order of Nidovirales, a Coronaviridae Family, Orthocoronaviridae is the Subfamily and are classified in the Genres: *Alphacoronavirus* (α-COV), *Betacoronavirus* (β-COV), *Deltacoronavirus* (γ-COV) and *Gammacoronavirus* (γ-COV).[2]

Among the identified coronaviruses, SARS-CoV-2 is the seventh identified to cause disease in humans,[2] and the third to determine an epidemic after severe acute respiratory syndrome (SARS-CoV) and Middle Eastern respiratory syndrome (MERS-CoV), which severe airway symptoms occurred and has a high mortality rate (10%-30%). The other four, considered endemic (HKU1, OC43, 229E, and NL63), have mild cold-like symptoms and are responsible for approximately 10% of seasonal airway diseases which are not caused by influenza.[3]

SARS-CoV-2 is a β-COV, like MERS-CoV and SARS-CoV, and has a genomic similarity of about 50% and 80%, respectively. The homology model showed that the structure of the SARS-CoV and SARS-CoV-2 receptor binding region is quite similar, suggesting the same pathogenesis. Authors confirmed that SARS-CoV and SARS-CoV-2 enter the host cell by binding its *S* proteins to the angiotensin 2 converting enzyme (ECA2) receptors, located on the cell surface. The ECA2 receptor has been described in several cells, including those of the gastrointestinal system, which can lead to related symptoms.[11]

Researchers used cryoelectronic microscopy to

demonstrate the molecular structure of the new coronavirus S protein and found that the affinity between SARS-CoV-2 and ECA2 is 10 to 20 times larger than SARS-CoV.[2]

Incidence

The number of infected cases varies greatly in different countries, depending on the measures being taken, which depends on diagnostic tests, social distancing, the population, level of education and government measures.[8]

The speed of increased number of cases and deaths is high. The Centers for Disease Control and Prevention (CDC) observed that the territory of the USA reached quickly in two months, 1/3 of the world's cases, which was reduced to 1/4 of the world's cases in July/2020, due to the growth of cases in other countries.[8] In Brazil, the first case was confirmed at the end of February/2020, initially growing in a "controlled" way due to mitigation and suppression measures. However, due to serious failures of the federal government, with an unprecedented political crisis, which led to the dismissal of two health ministers, and their insistence on maintaining a negative narrative, with speeches contrary to the recommendations of researchers and national and international institutions regulating health, we reached at the end of September/2020 with almost 5,000,000 cases and more than 142,000 deaths.[9] However, the number of cases is even higher, and it is estimated that it should be multiplied by six.[12]

The number of deaths is also underestimated. Considering the data from the *Sistema de Informação da Vigilância Epidemiológica da Gripe* (SIVEP) (Epidemiological Surveillance Information System of Influenza) in Brazil,[13] there were almost 50,000 deaths, at the end of August/2020, due to unspecified acute respiratory syndrome (SARS), since they were not tested for COVID-19.

Of the number of cases in Brazil, the Southeast Region always presented the highest number, followed by the Northeast, North, South and Mid-West regions. The epicenter of the disease started in the State of São Paulo, followed by the States of Amazonas, Ceará and Pernambuco, and in September, it remained in São Paulo, followed by Bahia, Minas Gerais and Rio de Janeiro.[9]

Epidemiology

The epidemiology of the disease differs according to the country, as prevention measures directly influence the number of cases and death. Some factors associated with COVID-19 were suggested, such as biological and socio-demographic, as well as economic, organizational and health system resources. Men are more frequently and severely affected than women, the average age is 47 years old and most deaths involve individuals over 70 years of age and with associated chronic diseases, being generally mild in children and adolescents.[14] However, cases of Multi-Systemic Inflammatory Syndrome in Childhood associated with COVID-19 have been described, some are fatal.[15]

In a study conducted in 57 countries, the main factor associated with mortality was the highest number of cases per day.[16] At this time, there was only one case in Brazil. Thus, with the increase in the number of cases, especially in countries with different socioeconomic reality, other factors were discovered,[9] such as in pregnancy.[17,18]

Among the strategies to prevent an epidemic, there is suppression and mitigation. By definition, suppression aims at keeping the number of cases to an absolute minimum, for as long as possible, through early and effective control interventions, until the emergence of the vaccine or treatment. While mitigation, control of the epidemic would occur with immunity acquired gradually, in order not to overload - to a point of collapse - the health system.[19]

Countries such as China and South Korea have managed to adopt a suppression strategy, with intense and extreme measures, such as forced quarantine, contact tracing and electronic surveillance of citizens' movements. However, in the Western democracies, there was a concern about the feasibility of these measures, even for high-income countries.[19] Mitigation strategies, such as suspension of classes and cancellation of flights, have been adopted by several countries, including unprecedented measures such as the production of health suppliesin a war regime, personal protective equipment (PPE) and respirators.[20]

Thus, in the absence of medications or vaccines, the alternative to prevent the collapse in the health systems was to combine a policy of social isolation with universal testing. Even with the return to the "new normal" in countries that have theoretically managed to control the pandemic, broad-based testing is essential along with preventive measures, such as the use of masks and hygiene measures and respiratory etiquette, according to WHO recommendations.[21]

Countries that have carried out mass population testing in having to control the epidemic and reduce the virus lethality rates, such as in South Korea.[20] However, in Brazil the projection is that, with the methodology of testing only severe cases, one out of

every five and one out of every 10 infected cases are detected, since 79% of the infections are transmitted by asymptomatic individuals. Mathematical modelling has been done, estimating that the number of infected people when only severe cases are tested, can be five to 30 times higher.[22]

Social distancing decreases the spread of the virus, reducing the number of victims and disrupting health services. Countries that have adopted this measure have experienced a faster decline.[21] In Brazil, health authorities in each state, city, and federal district have made decisions about the adoption or relaxation of distancing, being responsible for daily monitoring and weekly reassessment.

Other protective measures to reduce the spread of the disease include hand washing, use of alcohol gel at 70%, use of masks and respiratory tag, covering the mouth with the forearm when coughing or sneezing. It is recommended to put on a mask that allows the mouth and nose to be covered, avoiding touching it. There are several models of masks in the market, and its use depends on each situation.[21] More recently, the use of fabric masks by the entire population has been recommended, including children from five years of age.

As for seroprevalence, in Brazil some studies show to be a relatively increased in different Brazilian cities, with alarming numbers in cities such as Boa Vista (Roraima) - 25.5%, Sobral (Ceará) - 22.1%, Tefé - 20.3% and Imperatriz (Maranhão) - 16.5%.[12]

Transmission route

Epidemiological studies describe that three conditions are related to the spread of viruses: source of infection, transmission route, and susceptibility.[2] SARS-CoV-2 is a highly transmissible virus. The main transmission occurs through droplets (large particles >5 mm, moving 1-2 meters) that originate when an infected person sneezes or coughs. Aerosol transmission (small particles <5mm, moving more than 1 meter) is possible, but controversial. In the absence of evidence, preventive measures are suggested, since this transmission route, if confirmed, is especially relevant in the health field.[3] Transmission through contact with surfaces or sources contaminated by droplets is also relevant, when touching these surfaces and, subsequently, taking the hands to the nose, eyes or mouth, but there are no specific reports demonstrating this type of transmission.

Although, it has been detected in other biological samples, including urine and feces, to date there are no published reports of fecal-oral transmission of SARS-CoV-2.[2] Similarly, the role of blood transmission remains uncertain. The detection of low plasma and serum viral titers suggests little risk of transmission via this route.

The transmissibility of the virus is calculated by R0, the ability of the virus to be transmitted in one person's body to the others. Authors suggest that this calculation is important for the epidemiology of COVID-19, although studies have performed the calculation without adequately screening all, or even a significant percentage of contactors. For SARS-CoV-2, an R0 of 2.47-2.86 has been estimated, usually three.23 However, evidence suggests that this number may be higher, a median of 5.7.[24] The median may not reflect the extremes and may fail to consider "superspreading" individuals, such as the South Korean patient,[31] responsible for the contamination of more than 1,000 people.[25]

Incubation period

The average incubation period of SARS-CoV-2 of five days is considered, ranging from zero to 14 days, shorter than that are SARS-CoV and MERS-CoV. Studies found a median incubation period of 5.0 to 6.5 days, ranging from zero to 24 days.[24,26] This long incubation period may favor an increased risk of transmission.[24] The median onset of symptoms at death was 14 days, and 97.5% of patients develop symptoms within 11.5 days of infection.[24,26]

Clinical Presentation

The clinical frame of patients infected by SARS-CoV-2 is very varied, ranging from asymptomatic patients to mild to severe ones. Approximately 80% of the cases are mild to moderate with spontaneous cure. The frequency of asymptomatic cases is still unknown.[27]

The most frequent clinical symptoms are fever (87.9%), coughing (66.7%) and fatigue (38.1%).28 Other symptoms include dyspnea, headache, asthenia, myalgia, odynophagia, nasal congestion/discharge, anosmia, ageusia, syncope, confusion, conjunctivitis, dry eye and rash.[1] A lower percentage of patients report diarrhea, vomiting and abdominal pain as relevant symptoms.[28,29] (Table 1). In one study, gastrointestinal symptoms were present in 11.4%[30] and in another, neurological manifestations were observed in 36.4% of the patients, in addition to cardiac manifestations such as arrhythmias and hepatic dysfunction in up to 50% of the cases.[2]

Dyspnea, with variable severity, is present in most patients seeking hospital medical assistance, as this would be the moment when pneumonia and SARS begin to complicate with the flu.[2] It is impor-

tant to note that not all cases of COVID-19 develop pneumonia. The time from the onset of the symptoms to the development of severe lung condition, it is required Assisted Mechanical Ventilation (AMV) varies from seven to 14 days (median of 10.5 days).[31]

Authors suggested that 13.8% of the cases, which were considered severe, had shortness of breath, respiratory rate ≥30 per minute, blood oxygen saturation ($SatO_2$) ≤ 93%, arterial oxygen pressure (PaO_2)/inspired oxygen fraction (FiO_2) ratio <300 mmHg and/or radiologically proven pulmonary infiltrates. In addition, 6.1% of SARS-CoV-2 infections, there was a critical course associated with respiratory failure, septic shock and/or multiple organ failure.[28] Other complications were reported, such as pulmonary thromboembolism, neurological and cardiac disease, and clinical investigation for each disease is prudent.[32]

Laboratorial Diagnosis

Reverse transcription-polymerase chain reaction (RT-PCR)

Molecular diagnosis of infections is based on RT-PCR techniques that identify specific sequences of the SARS-CoV-2 genome. In general, it is recommended to detect a less specific area as screening (the envelope gene or the *E* gene) and another more specific area for confirmation (RdRp RNA polymerase gene). However, there are different combinations of sequences, according to the technique developed by the laboratories, leading to different rates of sensitivity and specificity. Despite the high sensitivity and specificity, these tests can present false negatives.

It is noteworthy that without a gold standard test available, it is difficult to determine the validity of diagnostic tests, including sensitivity, specificity, positive and negative predictive values. It is suggested that Computed Tomography (CT) may be considered the gold standard for this validation.[33]
The false negative result usually occurs because the sample is insufficient or unrepresentative, the test was performed early or late in the course of the disease, or the sample was degraded during transport or handling.[34] If the initial test is negative in a patient with a strong suspicion, the patient should be resampled, with a time interval of at least one day and/or samples collected at different sites in the respiratory tract (nose, sputum and endotracheal). Additional samples, such as blood, urine and feces, may be collected to monitor the presence of the virus and its release. When the RT-PCR for SARS-CoV-2 is negative for two consecutive tests, the COVID-19 can be discarded.[35] A study of pharyngeal samples observed potentially unstable results and was not considered the only indicator for diagnosis, treat-

Table 1

Typical signs of SARS-CoV-2 infection.

Symptoms	Frequency (%)
Coughing	86.1
Fever	85.0
Dyspnea	80.0
Ageusia/dygeusia	57.1
Anosmia/hyponosmia	55,4
Mialgia	34.4
Diarrhea	26.7
Nausea/vomiting	24.4
Sore throat	17.8
Cephalea	16.1
Nasal congestion	16.1
Thoracic pain	15.0
Chills	11.4
Abdominal pain	8.3
Sibilance	6.7
Mental and/or confusion alterations	6.1
Eye Manifestation	4.3
Hemoptyse	0.9

Source: Adapted from the World Health Organization.[28]

ment and isolation, recovery/high and transfer to hospitalization of clinically diagnosed patients. In the course of the pandemic, it is recommended that clinical-epidemiological criteria should be used for diagnosis, treatment, and case reporting.[36]

The lower respiratory tract samples probably have a higher diagnostic value compared to those in the upper tract, but require greater care with biosecurity. If patients show no signs or symptoms of lower respiratory tract disease or if the collection is not possible, swabs from combined or unmatched upper respiratory tract samples, nasopharyngeal and oropharyngeal, should be collected.[37]

Lack of sensitivity, insufficient stability, and long processing time of the RT-PCR SARS-CoV-2 may be limiting in a pandemic situation, but it is the test of choice for diagnosis. The need to supply this test is critical to conducting the pandemic and resuming day-to-day "new normal" activities.

Rapid test and antibody detection

There are two rapid testing techniques: nasopharyngeal swab and/or oropharynx for viral antigen detection; and detection of antibodies in whole blood, serum, and plasma samples.[35]

The rapid test through the nasopharyngeal swab and oropharynx uses the RT-PCR technique. It is recommended that it should be collected simultaneously. Unlikely the blood test, the collection should be done as soon as possible after identification of the clinical suspicion, disregarding the time of the onset of the symptoms. The rapid test has less sensitivity than the conventional RT-PCR.

The detection of antibodies of immunoglobulin classes A (IgA), M (IgM) and G (IgG) against SARS-CoV-2, in samples of whole blood, serum and plasma, by the rapid test or not, is performed through the technique of Enzyme-Linked Immunosorbent Assay (ELISA), chemiluminescence and electrochemical chemiluminescence.

In cases of COVID-19, IgA is more sensitive than IgM, 92.7% and 85.4%, respectively. Around the 5th day of appearance of the symptoms, acute phase of the disease, it is possible to detect these antibodies, as well as the cross-positivity by other viruses. Specifically IgG is evidenced around the 10th to the 18th day after the appearance of the symptoms and appears with a sensitivity between 67% and 78%.[38]

A diagnostic validation study suggests that the serological test has a high positive predictive value and a low negative predictive value in the acute phase of the disease, in the first seven days of the symptoms. The use of this test for early diagnosis is not feasible, but can be used when the suspicion is late. In the acute phase, there is no presence of neutralizing antibodies, which are seroconverted between days four and nine of the infection, with IgM peak on the ninth day after the onset of the disease, and IgG in the second week.[38]

The choice of the test to be requested is based on the time of thesymptoms and the availability of the laboratory (Figure 1). It is important to note that its interpretation must be performed by a qualified professional (Table 2).[39]

Cell Culture

Cell culture is another diagnostic medium from nasopharyngeal aspiration through daily observation by electron microscopy. In positive cases the virion particle is identified as belonging to the Coronaviridae family.

Cell culture for diagnosis of SARS-CoV-2 is time-consuming and not useful for clinical diagnosis, particularly in pandemic situations, and is reserved for research.[34] On the other hand, it is considered the only laboratory method capable of determining the presence of cytopathogenic viral agents, proving infectivity, especially in cases of emerging viruses. In special situations, such as the detection of viral particles, for example in breast milk or individuals following positive RT-PCR weeks after infection, viral culture may be employed to determine infectivity or potential transmission.[34]

Recommendations

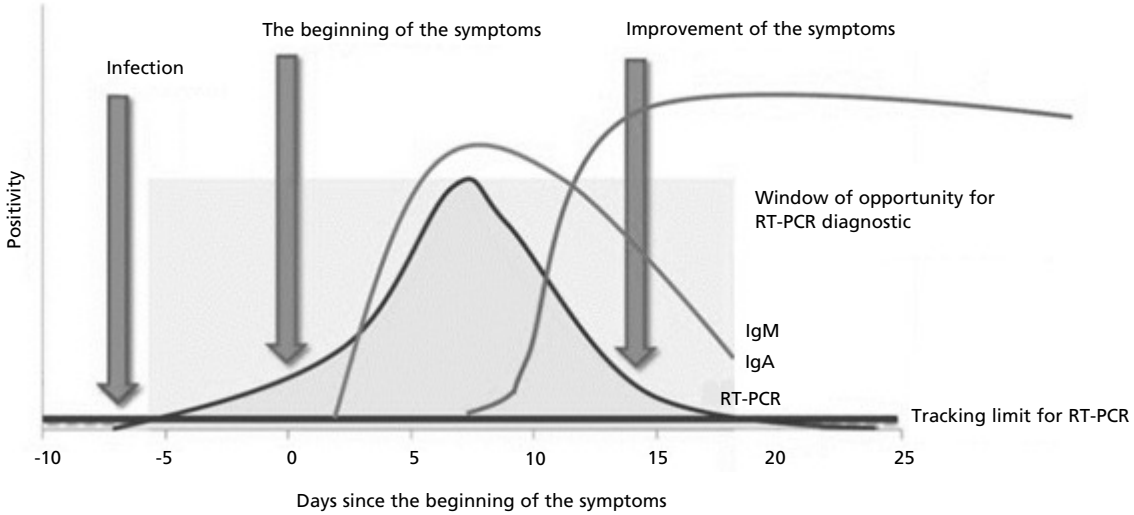
WHO recommends for the diagnosis, the performance of RT-PCR for SARS-CoV-2 in all symptomatic patients. RT-PCR testing of asymptomatic individuals can be considered in the management of individuals who have had contact with COVID-19 and can be adapted to the realities of each location.[37,40]

In Pernambuco and Paraíba, and in other states of Brazil, the recommendation is that the collection of ARDS in the nasopharyngeal and oropharyngeal secretions should be performed, using three swabs (two for the nasopharynx and one for the oropharynx). These should be packed in the same viral transport and sent to the *Laboratórios Centrais de Saúde Pública* (LACEN) (Central Public Health Laboratories) with the ARDS form and registration in the *Gerenciador de Ambiente Laboratorial* (GAL) (Laboratory Environment Management). The collection must be done, preferably, until the third day of the beginning of the symptoms and can be done until the seventh day.

According to the Brazilian Ministry of Health,

Figure 1

Laboratorial tests result for SARS-CoV-2, according to the day of the symptomatology.



Source: Dias *et. al*.[38]

the examination should be carried out based on the evaluation of clinical criteria performed by a health professional for the symptoms of influenza syndrome and ARDS and a history of close contact or at home with a confirmed diagnosis in the last seven days before the onset of the symptoms.[41]

Unspecific laboratorial findings

Authors described several non-specific laboratorial changes due to COVID-19, such as elevation in the number of leukocytes, interleukins (IL), C-reactive protein (CRP), lactate dehydrogenase (LDH), hemosedimentation velocity (HSV), liver transaminases and D-dimer. Hypoalbuminemia, lymphopenia (<1,100 cells/ml) in 82.1%, thrombocytopenia in 36.2% and leukopenia in 33.7% of hospitalized patients were also observed.[42]

Studies suggest that *IL-6* and D-dimer are markers of severity, with high sensitivity and specificity.[43] It should be noted that severe cases, compared to moderate cases, present more frequently with severe lymphopenia, hypoalbuminemia and elevation of alanine aminotransferase (ALT), LDH, CRP, ferritin, D-dimer, *IL-2R*, *IL-6*, *IL-10*, tumor necrosis factor alpha (TNFa)[44] and troponin.[45]

Image Examinations

Chest Radiography

The main manifestation of SARS-CoV-2 infection is pulmonary. Thus, chest radiography has been extensively studied, noting that the radiological findings of SARS-CoV-2 pneumonia are similar to any other community pneumonia.[31,46]

In the first two days of the symptoms, no alteration can be observed in a simple radiography and computed tomography (CT). As the condition evolves, the CT sensitivity increases, especially after the sixth day, when almost all patients with COVID-19 present some alteration.[46]

Asymmetric areas of alveolar or interstitial opacity, patched or diffuse can be identified in the simple chest radiography. The most common pattern is bilateral pneumonia, with subpleural frosted glass opacities, with ill-defined margins and a slight predilection for the right lower lobe (Figure 2A).[46]

Computed tomography of the chest

The use of CT in patients with COVID-19 has been used in the diagnosis and to assess the severity. The examination detects lesions that are not identified in a simple x-ray, representing the gold standard for evaluating pulmonary involvement, with a higher

Table 2

Evolution of laboratorial parameters and the relation with the clinic.

PCR	IgM	IgG	Probable clinical response	Observation
-	-	-	Negative	Possibility that the individual has not been infected and is susceptible to the disease. Chances of the individual being infected at the time of testing.
+/-	-	-	Incubation period of the virus/symptomatic	The body has not yet had time to produce antibodies by the immune system.
+	-	-	Immune window	It is not possible to detect the presence of immunoglobulins yet. The individual is probably transmitting the virus at the time of testing.
+	+	-	Initial phase of infection	Contact with the virus was recent. The individual is probably transmitting the virus at the time of testing.
+	+	+	Active phase of infection	There has been recent infection of the virus and antibodies are already in the transition phase. The individual is probably transmitting the virus at the time of testing
+	-	+	Final or late phase/recurrent infection	There has been infection and the individual can still transmit the virus. This result may also show a false negative for IgM.
-	+	-	Initial phase of disease	Contact with the virus was recent. This result may demonstrate a possible false negative PCR result.
-	-	+	Serological scar	The individual has been infected by the virus and probably has immunity against the disease and does not transmit the disease.
-	+	+	Active phase of infection	There has been infection and antibodies are still in the transition phase. This result may demonstrate a possible false negative PCR result.

Source: Adapted from Francisco and Canga.[39]

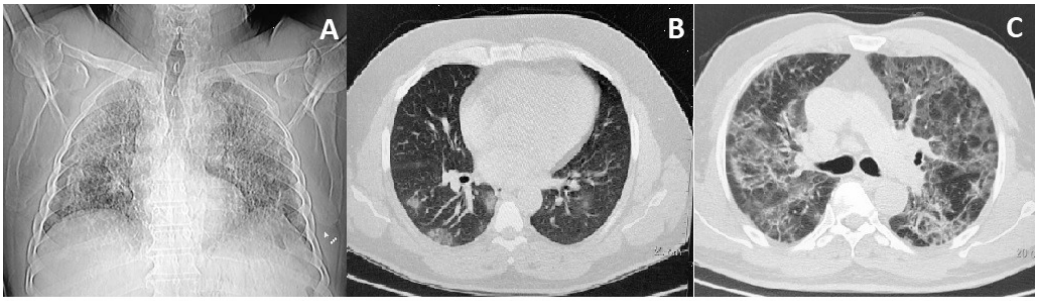
sensitivity than the RT-PCR.[47] This may be relevant in the early identification of the cases, for example, in preoperative patients with clinical suspicion of the infection.

CT findings are earlier than radiographic ones, and may be present even in patients without important clinical manifestations. The main alterations are opacities with frosted glass pattern (65.0%), consolidations (50.0%), thickening of interlobular septa (35%), aerial bronchogram (47%) and thickening of the underlying pleura (32%), with predominance of inferior and peripheral lobes involvement and generally bilateral (Figures 2B, 2C).[31,47]

The sensitivity and specificity of RT-PCR and CT in a study of patients with suspected of COVID-19 varies according to different publications. In a systematic review was observed that CT and RT-PCR have high sensitivity (94% and 89%, respectively), while the specificity of CT is low compared to RT-PCR (37% and 95%, respectively). This

Figure 2

Radiological (A) and tomographic (B and C) aspects of a patient with COVID-19.



A) Anteroposterior chest radiography, presenting diffuse bilateral infiltrate with interstitial pattern. B) Chest tomography, presenting consolidation at the base of the right lung (secondary pneumonia?). C) Chest tomography, presenting a frosty glassarea typical of SARS-CoV-2 infection.
Source: Rodrigues *et al*.[46]

decreases the positive predictive value of CT, especially in low prevalence scenarios (<10%), and can be up to 10 times lower than the RT-PCR. The negative predictive value (NPV) of both tests is, however, high (>99.0%).[48]

Thus, the use of CT as a universal screening method, or on asymptomatic patients, in populations with low prevalence, may present a low detection rate and, consequently, an increase in unnecessary exams and medical expenses, besides generating anxiety in patients. It should be noted that it is an exam that increases the radiation dose in the population. In a high prevalence scenario, the use of CT can be supported by its high NPV, especially in situations where a quick decision must be made, and rapid tests are not available. However, there are no studies on the cost-effectiveness of this measure.[48]

Pulmonary ultrasonography

Pulmonary ultrasonography was suggested as a tool to detect pulmonary involvement in COVID-19. Some advantages are: possibility of being performed at bedside, by a single operator, reducing the risk of contamination among health professionals; it does not emit radiation and can be used in pregnant women; and ease in monitoring patients who need serial exams.[49]

Definition of case - SARS-CoV-2

WHO published on 03/20/2020 the diagnostic criteria of a suspect, probable and confirmed case for COVID-19:[40]

1. Suspicious case
   •Patient with acute respiratory disease, characterized by fever and at least one respiratory sign or symptom (e.g., coughing and shortness of breath) **AND** a history of traveling, or residing, at a location with community transmission of COVID-19 for 14 days before the onset of thesymptoms; **OR**
   •Patient with any acute respiratory disease **AND** having been in contact* with a confirmed or probable case in the last 14 days before the onset of the symptoms; **OR**
   •Patient with acute respiratory disease, requiring (severe) hospitalization **AND** absence of alternative diagnosis that explains the clinical presentation.

2. Probable case
   •Suspicious case with inconclusive laboratorial tests; **OR**
   •Suspicious case with laboratorial tests not performed for any reason.

3. Confirmed case
   •Person with laboratorial confirmation, regardless of clinical signs and symptoms.

* Contact is defined as a person who has experienced any of the following exposures during the previous two days and the 14 days after the onset of a probable or confirmed case symptoms:
   •Face-to-face contact within one meter and for more than 15 minutes;
   •Direct physical contact;
   •Direct patient care, without the use of appropriate personal protective equipment (PPE);
   •Other situations, as indicated by local risk assessments.
   •If confirmed asymptomatic, during the indi-

cated period and from the collection of the sample that confirmed COVID-19.

The Brazilian Ministry of Health defines suspicious cases by the following classification[41]:

1. Influenza Syndrome (IS)

Patient with acute clinical frame with the presence of at least two of the following symptoms:

o Chills;
o Fever (even if mentioned);
o Sore throat;
o Cephalea;
o Coughing;
o Runny nose;
o Olfactory or taste disorders.

Observations:

•Children: nasal obstruction should also be considered in the absence of other specific diagnoses;

•Elderly: specific criteria for aggravation, syncope, mental confusion, excessive sleepiness, irritability and inappetence are considered;

•Gastrointestinal symptoms (diarrhea) may be present.

2. ARDS

Patient diagnosed with IS and evolves at least one of these signs below:

o Dyspnea and/or respiratory discomfort;
o $SatO_2$ <95% in ambient air;
o Persistent pressure in the chest;
o Bluish coloring of the lips or face.

Observations:

•Children: one should also consider nose wing beats, cyanosis, intercostal retractions, dehydration and inappetence;

•For the notification cases, the cases of ARDS hospitalizations or deaths by ARDS regardless of hospitalization should be considered.

The disease can also be classified according to severity criteria (Table 3).

Stages of COVID-19

Although the details of cellular responses are not known, a likely course of events may be postulated based on previous studies with SARS-CoV. The pathogenesis describes three distinct phases[50]:

•Viral replication phase - usually asymptomatic starts in the first days, one to two days. SARS-CoV-2 binds to the ECA2 receptor of the epithelial cells of the nasal cavity, initiating its replication, first in the ciliated cells. There is local viral spread, but the innate immune response is limited. The RT-PCR value can be useful to predict viral load and subsequent infectivity and clinical course. At this stage the viral load is low, but patients are infective and the diagnosis can be made by nasal swab.

•Inflammatory phase - in the subsequent days there is an inflammatory response of the upper airways and the conductors. The virus migrates to the conductive airways and starts the most robust innate immune response, producing inflammatory cytokines. The infected epithelial cells are an important source of interferons. In this period, detection by nasal swab, sputum and markers of innate response are more likely. The innate immune response may improve predictions about the course of the disease and the need for more aggressive monitoring.

• Hyperinflammatory phase - tissue hypoxia occurs with frost-glass opacity of the lung on the X-ray, progressing to Acute Respiratory Distress Syndrome (ARDS) in 15%-20% of the individuals. The virus reaches gas exchange units, infecting and destroying type II pneumocytes, usually in peripheral and subpleural areas, resulting in diffuse alveolar damage, with formation of hyaline membrane rich in fibrin and leading to a cycle of aberrant damage/repair that can culminate in fibrosis more rapidly than other forms of ARDS. The virus spreads, large numbers of viral particles are released, and most cells suffer apoptosis and die. The recovery will require vigorous innate and acquired immune response and epithelial regeneration. The elderly are at risk for the decreased immune response, reduced ability to repair the epithelium and less mucociliary clearance, allowing the virus to spread more rapidly.

Treatment

So far, reviewing the literature, one can conclude that there is no scientific evidence to recommend any treatment for COVID-19 in the early phase. Although, there is no treatment approved by the Food and Drug Administration (FDA) in many countries physicians are prescribing several medications without scientific evidence.[51]

Currently, based on in vitro studies on the suppression of SARS-CoV-2 activity and studies on other strains of coronavirus, several medications have been used, following a line of treatment in order to inhibit different stages of replication: fusion (use of monoclonal antibodies and plasma from cured patients); endocytosis (chloroquine and hydroxychloroquine); translation (camostat mesilate); proteolysis (lopinavir-ritonavir and remivir);

Table 3

COVID-19 classification according to severity.

• Asymptomatic or pre-symptomatic infection: individuals who tested positive for SARS-CoV-2 but present no symptoms
• Mild illness: individuals who present any of the various signs or symptoms of COVID-19 (e.g. fever, coughing, sore throat, malaise, headache and myalgia), without dyspnea, tachypnea or altered imaging examinations.
• Moderate disease: individuals who present evidence of low respiratory disease by clinical evaluation (altered auscultation) or imaging and maintain oxygen saturation ($SatO_2$) > 93%.
• Severe disease: individuals who have respiratory rate (RR)> 30irpm, $SatO_2$< 93%, oxygenation index (PaO_2/FiO_2 ratio) <300 or pulmonary infiltrates >50%.
• Critical illness: individuals who have respiratory failure, septic shock and/or multiple organ dysfunction.

Source: National Institutes of Health; 2020.[36]

translation and replication of RNA; virion packaging; and virion release.[51]

WHO and some partners have launched SOLIDARITY, an international clinical trial to determine the effectiveness of different treatments, conducted in more than 400 hospitals in 35 countries: remdesivir; lopinavir/ritonavir; lopinavir/ritonavir associated with interferon beta-1a; and hydroxychloroquine.[52]

Numerous clinical studies on the treatment of COVID-19 have been registered. In August 2020, 3,379 studies were registered on the Clinical Trials platform. However, published research has been limited by theresults, short follow-up, eligibility criteria, small sample size and lack of evaluation on adverse effects. Although, randomised clinical trials are the ideal trial design, given the urgency, observational studies have been published and their results considered to assess clinical outcomes and adverse effects. For the use of these drugs in pregnant women, there is still a need to observe fetal safety, with the need for specific clinical research in pregnant women.[53]

The CDC and several national and international medical societies have published recommendations on the treatment, which are updated as more data are available.[36,54] WHO published in September 2020 a "living guideline" for the treatment of COVID-19, with emphasis on the use of corticosteroids for severe patients, intubated or receiving oxygen therapy, the only therapeutic modality that has proven effectively in reducing mortality.[55]

Chloroquine sulfate and hydroxychloroquine sulfatea

These drugs have been widely used for some forms of malaria, with hydroxychloroquine synthesized from chloroquine sulfateis the least toxic.[56]

Chloroquine is absorbed by the gastrointestinal tract and binds moderately (60%) to plasma proteins, undergoing biotransformation, by the liver system of cytochrome P450, into active metabolites. The derivatives of these metabolites will inhibit the protein synthesis, after inhibition of the DNA and RNA polymerase.[56] The anti-inflammatory action in autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, is not known.[56]

Although, they were initially included in hospital protocols, especially in critically ill patients, even without scientific evidence, both are not risk-free. Side effects are described, mainly cardiovascular, such as vasodilation, hypotension, decreased myocardial performance and arrhythmias, including QT prolongation and branch and atrioventricular (AV) block. These effects are dose-dependent and can cause death if they are high. Non-cardiovascular adverse effects reported are nausea, vomiting and diarrhea, thrombocytopenia, aplastic anemia, shock, seizures, hypokalemia, coma and death, even at usual doses. Of these, the most observed adverse cardiovascular effect is AV block, affecting up to 85% of the patients. It should be emphasized that most of these adverse effects return to normal with the suspension of the drug, however, in some cases, heart failure can be maintained for life.[57]

Care should be taken with the association of drugs, because interactions are not rare, such as with digoxin, insulin, oral hypoglycemic, antiepileptic, methotrexate, cyclosporine and drugs that prolong QT.[57]

The various national and international medical societies do not recommend its routine use, both in mild and severe patients.[36] However, following the recommendations and under pressure from the President of the Republic, the Brazilian Ministry of Health has expanded the access of patients to this treatment within the *Sistema Único de Saúde* (SUS) (Public Health System). Unfortunately, this was an exclusively political decision without scientific support, based on the interests of the negationist policy of offering a "magic" solution to reinforce the governmental decision of relaxing the rules on social distancing and taking the population to the streets with a false sense of security, besides the need of having a market to distribute millions of pills that, due to a miscalculation, have been manufactured by the Army laboratory since February/2020.

On June 20, 2020, the National Institutes of Health (NIH) discontinued the ORCHID Trial, with approximately 470 patients, after an interim analysis in which no beneficial effect of hydroxychloroquine was proven.[58] A study published in the New England Journal of Medicine also showed no beneficial effects using it for prophylaxis. The rationale of the drug was questioned after researchers demonstrated that its effect was only verified in VERO cells, because in these cells the only path to the virus is the endosome route, dependent on the acidity of the medium. As hydroxychloroquine alters the acidity of the medium, it prevents the entrance of the virus in the cell. However, when the drug was tested in specific cells of the respiratory tract, with an independent second pathway, hydroxichloroquine failed to block the entry of the virus into cell culture.

Hydroxychloroquine should not be administered in pregnancy, despite the insistence of the Brazilian Ministry of Health, as it is an undetermined class for FDA and class D of the Australian directive, it has been described mutagenic effects in vitro in animals and it is not possible to rule out malformations in humans. The drug should be used when the benefit overcomes the risk, as in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis and malaria, situations in which its effectiveness has been demonstrated and the disease carries greater risk than treatment.

Ivermectin

Ivermectin is an antiparasitic agent of broad spectrum that, in recent years, has been identified as having antiviral activity, *in vitro*. Recently, it was observed that the drug has inhibited SARS-CoV-2,[54] and *in vivo* studies are needed.

A multicenter, observational, prospective study conducted with patients diagnosed with COVID-19, in 169 hospitals, included 1,408 patients, divided into two groups: ivermectin (150µg/Kg) single dose; and usual therapy, without ivermectin. It was observed that overall mortality was lower in patients who used ivermectin, as in the same way mortality in the group of patients who required mechanical ventilation.[59] However, it was a pre-print publication that has not yet been peer-reviewed and there are no randomized clinical trials published proving the effectiveness and safety of this drug.

Ivermectin, according to recent meta-analysis, is class C in pregnancy and can only be used if the benefits clearly outweigh the risks.[60]

Lopinavir/ritonavir

The combination of protease, lopinavir and ritonavir inhibitors, used in HIV infection, was considered a potentially useful treatment because in vitro studies showed antiviral activity against SARS-CoV. In a randomized study with 199 critically ill patients, the additional use of lopinavir/ritonavir (400/100mg) was compared twice a day, associated with standard treatment only, and no decrease in the time for clinical improvement and the time for clinical deterioration was evidenced. The rate of SARS-CoV-2 declining was similar in both groups and the use of medication was interrupted at the beginning in 14% of the patients due to gastrointestinal adverse effects. In two patients, a serious adverse event (acute gastritis) was observed.[61]

Remivir is an adenosine analogue (pro-nucleoside analogue drug) that incorporates the viral RNA chains and prevents the action of viral polymerase through the premature termination of RNA transcription.[40]

The NIH has recommended its use and although it is not approved by the FDA, its emergency use is authorized totreat adults and children with severe conditions, and its effectiveness in clinical trials is being investigated.[62]

Preliminary data from a multicenter, randomized trial, which included 1,062 hospitalized patients, observed shorter clinical recovery time and lower mortality rate (6.7% x 11.9%; Hazard Ratio= 0.55; CI95%=0.36-0.83) with the use of remivir compared to placebo.63 On the other hand, another multicenter, randomized trial, which included 237 patients, showed no difference in clinical improve-

ment time. However, the study was terminated early, resulting in a small sample size, and the use of concomitant drugs (corticosteroids, lopinavir/ritonavir and interferon) may have obscured the effects of remdesivir.[64]

A systematic review published in September/2020 suggested that remdesivir may be beneficial in treating patients with COVID-19 but the quality of evidence is low. As the drug is very expensive and dexamethasone is cheaper, safer and more effective, remdesivir should be reserved for research protolocols.

Tocilizumab and Sarilumab

The cytokine storm, called cytokine release syndrome (CRS), is the main cause of morbidity in critical patients with COVID-19, because it is involved in the pathogenesis of organ failure leading to death. The virus activates different immune cells, such as macrophages, monocytes and dendritic cells, leading to secreting pro-inflammatory cytokines, such as *IL-6* and others.[65]

Tocilizumab inhibits the *IL-6* receptor and reduces the production of cytokines, being used in the acute phase of rheumatologic diseases. *IL-6* is induced by inflammatory stimuli and mediates various immune responses, resulting in decreased oxygen diffusion. The respiratory muscles become fatigued, which can lead to respiratory failure.[65]

Some observational studies and case reports have described the use of tocilizumab in critically ill patients, observing improvement in respiratory and laboratory parameters, such as ferritin, C-reactive protein and D-dimer levels, as well as alterations in the CT. For more evidence, studies are being conducted.[66]

Sarilumab can also be used for the therapeutic purpose of acting on cytokines in patients with COVID-19. It is a human monoclonal antibody and IL-6 antagonist. Clinical trials using the drug have been initiated.[67]

For NIH, the current data are still insufficient to recommend the use of *IL-6* inhibitors in the treatment of COVID-19.[40]

Interferon beta 1B and interferon alpha 2B

Interferons are cytokines that modulate the immune response by various mechanisms and are used in the treatment and control autoimmune diseases.

In a randomized study with 127 adults, at first non-severe, it was observed that in the intervention group, there was less time for nasopharyngeal swab test negation, clinical improvement, hospital discharge and transmissibility. However, these are intermediate outcomes that are not associated with reduced mortality and, therefore, more studies are needed.[68]

Plasma from cured patients

The use of convalescent plasma was recommended as an empirical treatment during the outbreaks of Ebola, MERS-CoV and H1N1 viruses. A series of cases described the administration of convalescent plasma in five patients with severe COVID-19. There was a decrease in the nasopharyngeal viral load, a decrease in the severity score and an improvement in oxygenation after 12 days of plasma transfusion.[69] However, the limited sample size and study design prevent us from stating the efficacy of this treatment.

In a systematic review available in the Cochrane library, which included eight studies (seven case series and one single-arm intervention study) with 32 participants, concluded that the evidence is of low quality in recommending this therapy.[70] Similarly, a randomized clinical trial that included 103 patients with COVID-19 did not show a statistically significant improvement in the use of convalescent plasma.[71]

Dexamethasone

Since the publication of the results of RECOVERY Trial, it has been suggested that dexamethasone should be used in the treatment of severe forms of COVID-19. The drug has reduced by 1/5 the mortality in patients requiring oxygen use and by 1/3 in patients undergoing mechanical ventilation, but has not been effective in the recovery of mild cases. The rationale for using dexamethasone is justified by the hyperinflammatory reaction that can be attenuated with corticotherapy.[50] Glucocorticoids cross the placenta and have been widely used in obstetrics, being class B according to FDA, not existing any contraindication.

WHO guidelines report that the only drug recommended for the treatment of patients with COVID-19 is dexamethasone or, alternatively, other corticosteroids such as hydrocortisone and methylprednisolone, and its use should be restricted to critically ill patients (Table 4).[55]

Prognosis

The prognosis of COVID-19 is variable and dependent on several factors. Although, most people with COVID-19 develop a mild (40%) or moderate (40%)

disease, approximately 15% develop a severe disease, with complications such as respiratory failure, SARS, sepsis and septic shock, thromboembolism, and multiple organ failure, including renal and cardiac failure.[40]

Some prognostic factors are inherent to the patient, such as pregnant women, immunosuppressed, patients >60 years of age and presence of comorbidities, especially cardiovascular disease and diabetics, which characterize patients in this risk group (Table 5).[65,72]

Mortality rates are heterogeneous, depending on the measures adopted. WHO suggests a rate of 3.8%, but it varies between 0.6% and 4.2%. These data are still speculative, because only with seroepidemiologic studies can determine the real prevalence of infection and, consequently, the mortality rate can be determined.[27] The high mortality rate in Italy can be justified because the Italian population is considered older and death related to COVID-19 in Italy is defined as a patient's death is the one who had a positive test. In other countries, a detailed clinical evaluation takes place, with the possibility that death was considered as the cause of comorbidities and not necessarily by COVID-19. Another point is regarding the policy of testing only severely ill patients, not notifying the mild cases, resulting in increased lethality.[72]

Final considerations

In view of the above, SARS-CoV-2 is a highly transmissible CoV that led to the current pandemic and the interruption of social and labor activities. There is still a limitation in the more precise understanding of the pathogenesis of SARS-CoV-2 in humans, which makes it difficult to identify viral and host factors. Currently, there is a difficult mission to develop and test antiviral interventions that will eventually control COVID-19 in humans. In this review, we detail the current understanding of SARS-CoV-2, the result of incredible efforts by researchers around the world.

Authors' contribution

Conception and design of the research: Souza ASR, Amorim MMR, Melo ASO, Katz L; Obtaining articles: Souza ASR, Amorim MMR, Melo ASO, Delgado AM, Florêncio ACMCC, Oliveira TV, Lira LCS, Sales LMS, Souza GA, Melo BCP, Morais I, Katz L; Evaluation and interpretation of the articles and manuscript writing: Souza ASR, Amorim MMR, Melo ASO, Delgado AM, Florêncio ACMCC, Oliveira TV, Katz L; Manuscript review: Souza ASR, Amorim MMR, Melo ASO, Delgado AM, Florêncio ACMCC, Oliveira TV, Lira LCS, Sales LMS, Souza GA, Melo BCP, Morais I, Katz L, NCOVIP; Critical review: Souza ASR, Amorim MMR. All authors approved the final version of this article.

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Table 4

Corticoids recommended for the pharmacological treatment of COVID-19.

Corticosteroid	Dosage (mg)
Dexamethasone	6
Hydrocortisone	50
Methylprednisolone	10
Prednisone	40

Source: Adapted from Lamontagne *et al*.[55]

Table 5

Risk factors of COVID-19.

Analytical alterations and risk factors of severity associated with a worse clinical evolution	
Severity markers	Risk factors for developing serious disease
Lymphopenia (< 1000)	Age >60 years
D- Dímer (>1000)	Hypertension
PCR	Cardiovascular disease
DHL	Pneumopathy
Ferritin	Diabetes
Creatinine	Obesity
IL-6 (cytokine storm marker)	Immunossuppression
Increase of transaminases	Cancer Pregnancy

Source: Adapted from Rubio-Pérez *et al*.[34]

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Received on Ocbober 1, 2020

Approved on December 9, 2020

ERRATA:

In Page S29, **Where it reads**:

"Northeast COVID-19 and Pregnancy Study Group (NCOVIP)"

Reading:

"Northeast COVID-19 and Pregnancy Study Group (NCOVIP)*"
*Study Group Members (NCOVIP) descripted at the end of the article.

Rev Bras Saúde Matern Infant. (2021) 21(Supl. 2): S565-S565.